Option Selection for Perchlorate Final Regulatory Action

Purpose:

- Obtain a decision on the final SDWA action for perchlorate to allow for timely agency review and to ensure meeting the consent decree deadline of June 19, 2020.

Background:

- Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches, and signal flares.
- Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States.
- Perchlorate can prevent uptake of iodide into the thyroid gland, which can affect thyroid hormone production.
- In some circumstances, changes in thyroid hormone levels in a pregnant woman may be linked to changes in the child's brain development.
- For infants, disruptions in thyroid hormone function can also impact brain development.

Proposed Rule:

- On June 26, 2019, the EPA released a notice of proposed rulemaking seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems.
- The EPA proposed a National Primary Drinking Water Regulation (NPDWR) for perchlorate with a Maximum Contaminant Level (MCL) and Maximum Contaminant Level Goal (MCLG) set at 56 micrograms per liter (µg/L).
- The proposed MCLG of 56 µg/L is based upon avoiding a 2 point IQ decrement in the most sensitive life stage (the fetus) for a specific segment of the population (iodine deficient pregnant women).
- The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate. Proposed monitoring requirements are consistent with the current standardized monitoring framework for inorganics and allow for monitoring waivers or reduced monitoring for systems with low or no occurrence following the initial round of sampling.
- The Agency requested comment on alternative MCL and MCLG values – 18 and 90 µg/L. These alternatives are based upon avoiding 1 point and 3 point IQ decrements in the most sensitive life stage for a specific segment of the population.
- The EPA determined that two systems would be required to take action to reduce levels below 56 µg/L, fifteen systems would be required to take action to reduce levels below 18 µg/L, and one system would be required take action to reduce levels below 90 µg/L.
- The EPA determined the benefits of the proposed rule <u>do not</u> justify the costs at the proposed or alternative MCLs.
- The Agency also requested comment on whether the EPA should withdraw the 2011 determination to regulate perchlorate.

Public Comments on Proposed Rule:

The public comment period on the perchlorate proposal ended on August 26, 2019, and EPA received a total of 1,495 comments in response to its rulemaking proposal.

<u>Mass Mailing Campaign:</u> 1,386 comments were received under a mass mailing campaign. These commenters oppose the proposed MCLG/MCL of 56 µg/L, stating that it is too high to adequately protect the health of communities.

Detailed Comment Letters from Organizations: 28 Comment letters addressing technical and policy issues were submitted. The overall recommendations of these comment letters on the regulatory proposal breakdown as follows.

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- None support the 90 µg/L alternative MCLG/MCL.
- Two support the 18 µg/L alternative MCLG/MCL:
    - Oregon
    - Virginia

- Fourteen support regulation at a MCLG/MCL lower than 18 µg/L:
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    - California
    - New Jersey
    - New York
    - Association of California Water Agencies
    - Metropolitan Water District of Southern California
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    - U.S. Conference of Mayors & the National League of Cities (joint letter)
    - California Farm Bureau Federation
    - American Water
    - El Paso Water
    - American Chemistry Council
    - American Water Works Association
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- 1 supports the withdrawal of the regulatory determination.
- 44 are in general opposition and/or out of scope.

Potential Options for Decision Making:

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Economic Analysis (Cost and Benefits):

Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

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420 µg/L[d]	$9.02	$0.00 ($0.00-$0.00)	$9.58	$0.00 ($0.00-$0.00)

Notes:

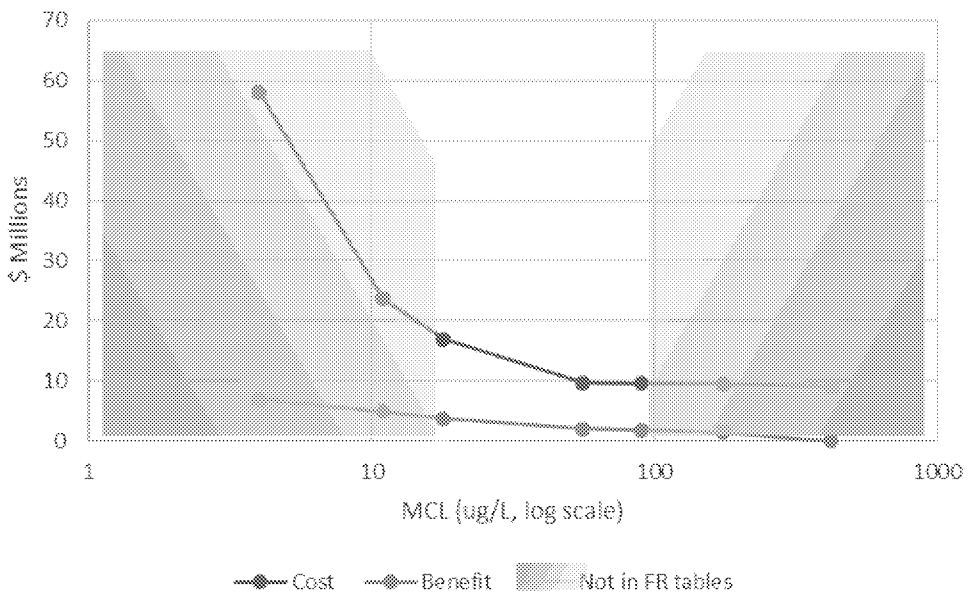
a. First benefit value reported is based on the central estimate of the gamma coefficient in: $\Delta IQ=(\gamma\times\ln(fT4_{rule}))-(\gamma\times\ln(fT4_{baseline}))$. The benefit range in parenthesis is based on the upper and lower bounds of the 95TH confidence interval around the gamma estimate.

b. EPA took comment on alternative MCLG/MCL of 18 and 90 µg/L.

c. EPA proposed an MCL of 56 µg/L

d. The highest perchlorate concentration observed in UCMR 1 is one sample at 420 ppb.

Chart for 3% Discount Rate Cost and Benefit Values



MCL (µg/L)	4	11	18	56	90	175	420
IQ loss	0.5	0.75	1	2	3	5	8.2

Ex. 5 AC/AWP/DP

Deliberative; Pre-decisional information, Internal EPA Document

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1/9/2020

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    - American Water
    - El Paso Water
    - American Chemistry Council
    - American Water Works Association
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    - Perchlorate Study Group
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Ex. 5 AC/AWP/DP

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Ex. 5 AC/AWP/DP

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APPENDIX

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Notes:
a. The benefit values are based upon avoided future income loss to the children who do not experience IQ decrements and discount rates have a significant effect on their magnitude.
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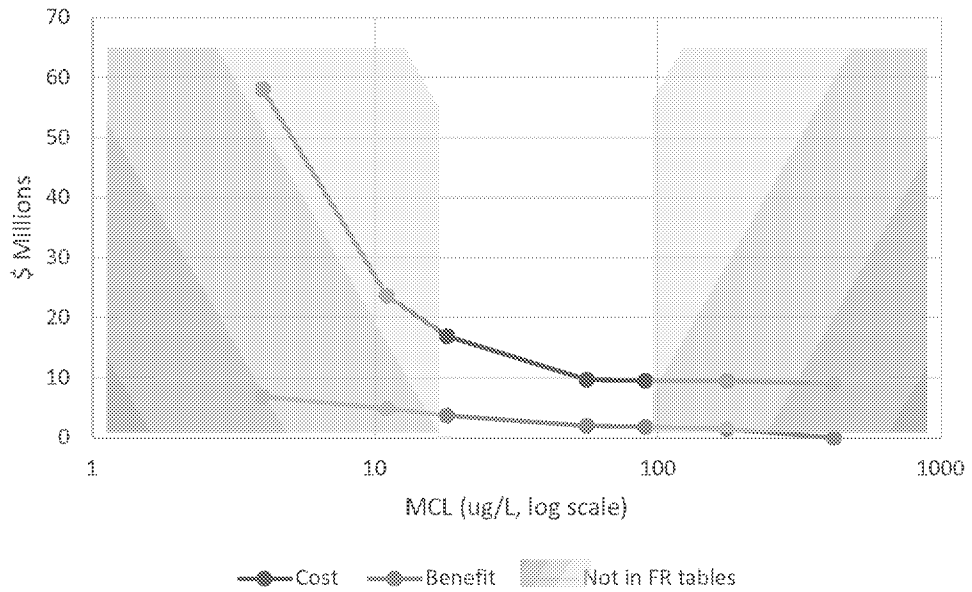

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ED_005043_00027773-00009

Message

From: Burneson, Eric [Burneson.Eric@epa.gov]
Sent: 1/8/2020 6:14:52 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
CC: Aguirre, Janita [Aguirre.Janita@epa.gov]; Mejias, Melissa [mejias.melissa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]; Nagle, Deborah [Nagle.Deborah@epa.gov]; Behl, Betsy [Behl.Betsy@epa.gov]; Wendelowski, Karyn [wendelowski.karyn@epa.gov]; Tovar, Katlyn [tovar.katlyn@epa.gov]
Subject: RE: revised perchlorate briefing
Attachments: Option Selection for Perchlorate 1-9-20v3 clean.docx

Attached please find a clean version of the briefing document in which I have:

- Accepted all of the edits from Lee and Charlotte with one modification noted in the next bullet.
- In Charlotte's edit to the considerations for Option 2, I deleted the word "may" since there were concerns

Deliberative Process / Ex. 5

- I deleted "Revised Draft" from the header and removed extra spaces in the document.

Please let us know if anything else is needed for OW submission to the A.O.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Forsgren, Lee
Sent: Wednesday, January 08, 2020 11:24 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Nagle, Deborah <Nagle.Deborah@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>
Subject: RE: revised perchlorate briefing

Jennifer here are my relatively minor edits incorporated into the edits Charlotte made.

From: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Sent: Wednesday, January 8, 2020 10:55 AM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Nagle, Deborah <Nagle.Deborah@epa.gov>; Behl, Betsy

<Behl.Betsy@epa.gov>; Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>
Subject: RE: revised perchlorate briefing

Thank you Charlotte for the quick response! We will turn this around quickly.
Lee – let us know if you have any additional comments.

Jennifer

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Wednesday, January 8, 2020 10:09 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Nagle, Deborah <Nagle.Deborah@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>
Subject: RE: revised perchlorate briefing

Thanks! I made a few tweaks in areas that I highlighted in green. Let me know if you are ok with those suggested changes. Looks good.
Cc'ing Lee for his input too.

From: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Sent: Tuesday, January 07, 2020 5:51 PM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Nagle, Deborah <Nagle.Deborah@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Wendelowski, Karyn <wendelowski.karyn@epa.gov>
Subject: revised perchlorate briefing

Charlotte
Attached is a revised perchlorate briefing document per our meeting with Dave this morning. I've also attached the track changes version so you can see the specifics of where we made changes.
Please let us know if you have any questions.
Jennifer

Jennifer L. McLain, Director
Office of Ground Water and Drinking Water
U.S. EPA

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1/9/2020

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Ex. 5 AC/AWP/DP

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Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Option 2b: Promulgate a final NPDWR for perchlorate at an MCLG/MCL of 18 ppb (1 IQ point decrement) while providing discretion to the states to determine which water systems are required to conduct monitoring (spring-in monitoring).

- Systems that found perchlorate in their finished drinking water previously would be required to perform monitoring for perchlorate.
- Other systems: states would determine which water systems are required to monitor by making determinations on the likelihood that a system is contaminated by perchlorate.

Rationale:

- System monitoring costs are reduced by assuming only some water systems, at state discretion, would be required to monitoring for perchlorate.

Legal Considerations:

- The proposal did not provide notice of such a change in monitoring, so it may be difficult to argue that a final action with such monitoring was a logical outgrowth of the proposal, and therefore there would be substantial legal vulnerability to a challenge under the APA.
- A monitoring option in which states choose whether and which systems monitor for perchlorate may be vulnerable to arguments that it is inconsistent with the structure of SDWA, which extensively depends on monitoring, and with the definition of the term ''primary drinking water regulation'' which means, among other things, a regulation which "contains criteria and procedures *to assure* a supply of drinking water which *dependably complies with such maximum contaminant levels*." Sec. 1401(1)(emphasis added).
- There would need to be a reasonable, factual basis to support or explain why monitoring would not be required for perchlorate if an MCL is established for it.
- If successfully challenged, the final regulation would likely be remanded to the Agency to seek public input on revised monitoring provisions or to promulgate different monitoring provisions.

Other Considerations:

- Same as Option 2 plus:
- There is an increased administrative burden for states due to the additional effort required to determine which systems must monitor.
    - There are many sources of perchlorate that states may consider in making this determination including fireworks, road flares, and missile contaminated sites.
    - A common drinking water disinfectant, sodium hypochlorite can degrade into perchlorate if it is improperly stored and/or managed. Limited data indicate that perchlorate levels resulting from disinfectant degradation in finished water would be at low levels (i.e., 0.1 – 2 µg /L)).
- States may expect the EPA to provide guidance on conditions that would compel monitoring at systems that have not previously conducted perchlorate monitoring.
- States and water systems may be reluctant to not monitor for a regulated contaminant.
- OGWDW estimates that this approach would reduce the costs of Option 2 by $3.02 to $3.35 million per year.

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

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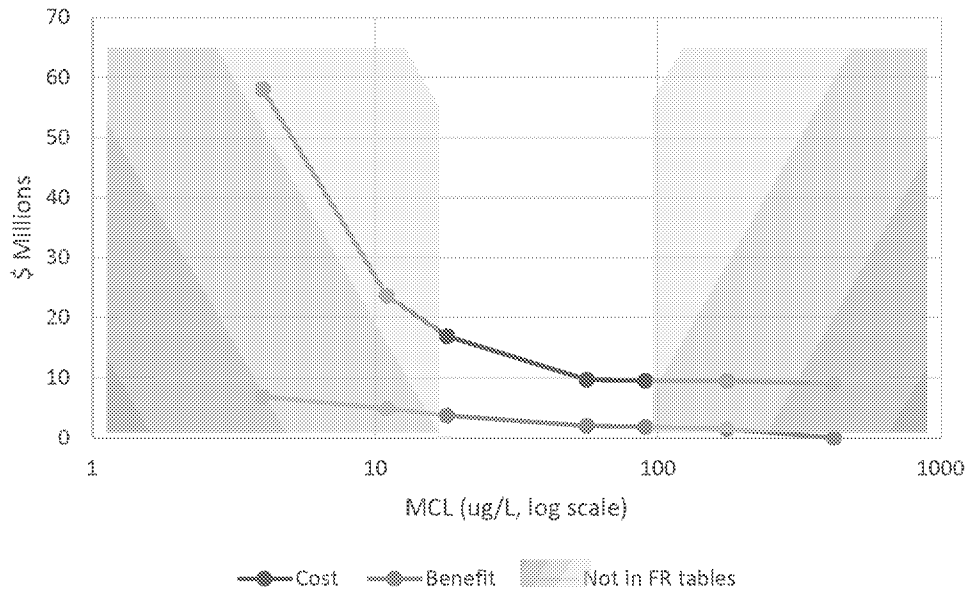
d. The highest perchlorate concentration observed in UCMR 1 is one sample at 420 ppb.

Chart for 3% Discount Rate Cost and Benefit Values



MCL (µg/L)	4	11	18	56	90	175	420
IQ loss	0.5	0.75	1	2	3	5	8.2

Option Selection for Perchlorate Final Regulatory Action

Revised Draft - 1/7/2020

Purpose:

- Obtain a decision on the final SDWA action for perchlorate to assure meeting the consent decree deadline of June 19, 2020.

Background:

- Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches, and signal flares.
- Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States.
- Perchlorate can prevent uptake of iodide into the thyroid gland, which can affect thyroid hormone production.
- In some circumstances, changes in thyroid hormone levels in a pregnant woman may be linked to changes in the child's brain development.
- For infants, disruptions in thyroid hormone function can also impact brain development.

Proposed Rule:

- On June 26, 2019, the EPA released a notice of proposed rulemaking seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems.
- The EPA proposed a National Primary Drinking Water Regulation (NPDWR) for perchlorate with a Maximum Contaminant Level (MCL) and Maximum Contaminant Level Goal (MCLG) of 56 micrograms per liter (µg/L).
- The proposed MCLG of 56 µg/L is based upon avoiding a 2 point IQ decrement associated with exposure during the most sensitive life stage (the fetus) within a specific segment of the population (iodine deficient pregnant women).
- The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate. Proposed monitoring requirements are consistent with the current standardized monitoring framework for inorganics and allow for monitoring waivers or reduced monitoring for systems with low or no occurrence following the initial round of sampling.
- The Agency requested comment on alternative MCL and MCLG values – 18 and 90 µg/L. These alternatives are based upon avoiding 1 point and 3 point IQ decrements associated with exposure during the most sensitive life stage within a specific segment of the population.
- Based on perchlorate occurrence data, the EPA estimated that two systems would be required to take action to reduce levels below 56 µg/L, fifteen systems would be required to take action to reduce levels below 18 µg/L, and one system would be required take action to reduce levels below 90 µg/L.
- The EPA determined the benefits of the proposed rule do not justify the costs at the proposed or alternative MCLs.
- The Agency also requested comment on whether the EPA should withdraw the 2011 determination to regulate perchlorate.

Public Comments on Proposed Rule:

The public comment period on the perchlorate proposal ended on August 26, 2019, and EPA received a total of 1,495 comments in response to its rulemaking proposal.

Mass Mailing Campaign: 1,386 comments were received under a mass mailing campaign. These commenters oppose the proposed MCLG/MCL of 56 µg/L, stating that it is too high to adequately protect the health of communities.

Detailed Comment Letters from Organizations: 28 Comment letters addressing technical and policy issues were submitted. The overall recommendations of these comment letters on the regulatory proposal breakdown as follows.

- None support the proposed MCLG/MCL of 56 µg/L.
- None support the 90 µg/L alternative MCLG/MCL.
- Two support the 18 µg/L alternative MCLG/MCL:
    - Oregon
    - Virginia

- Fourteen support regulation at a MCLG/MCL lower than 18 µg/L:
    - Massachusetts
    - California
    - New Jersey
    - New York
    - Association of California Water Agencies
    - Metropolitan Water District of Southern California
    - The Salt River Pima-Maricopa Indian Nation
    - The Tohono O'odham Nation
    - Alaska Community Action on Toxics
    - Environmental Defense Fund
    - Environmental Protection Network
    - Environmental Working Group
    - Natural Resources Defense Council
    - American Academy of Pediatrics

- Eleven support withdrawal of the determination to regulate perchlorate:
    - South Dakota
    - U.S. Conference of Mayors & the National League of Cities (joint letter)
    - California Farm Bureau Federation
    - American Water
    - El Paso Water
    - American Chemistry Council
    - American Water Works Association
    - Association of Metropolitan Water Agencies
    - National Rural Water Association
    - Perchlorate Study Group
    - The Chlorine Institute

- One organization did not take a position regarding regulation of perchlorate:
    - Association of State Drinking Water Administrators

Individuals: Eighty-one comment letters with varied levels of complexity were submitted by individuals. These letters cover a wide array of technical and policy issues regarding the perchlorate proposal. The overall recommendations of these comment letters on the regulatory proposal breakdown as follows.

- 6 support the 56 µg/L proposed MCLG/MCL.
- 1 supports the 90 µg/L alternative MCLG/MCL.

- 6 support the 18 µg/L alternative MCLG/MCL.
- 23 support regulation at an MCLG/MCL lower than 18 µg/L.
- 1 supports the withdrawal of the regulatory determination.
- 44 are in general opposition and/or out of scope.

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

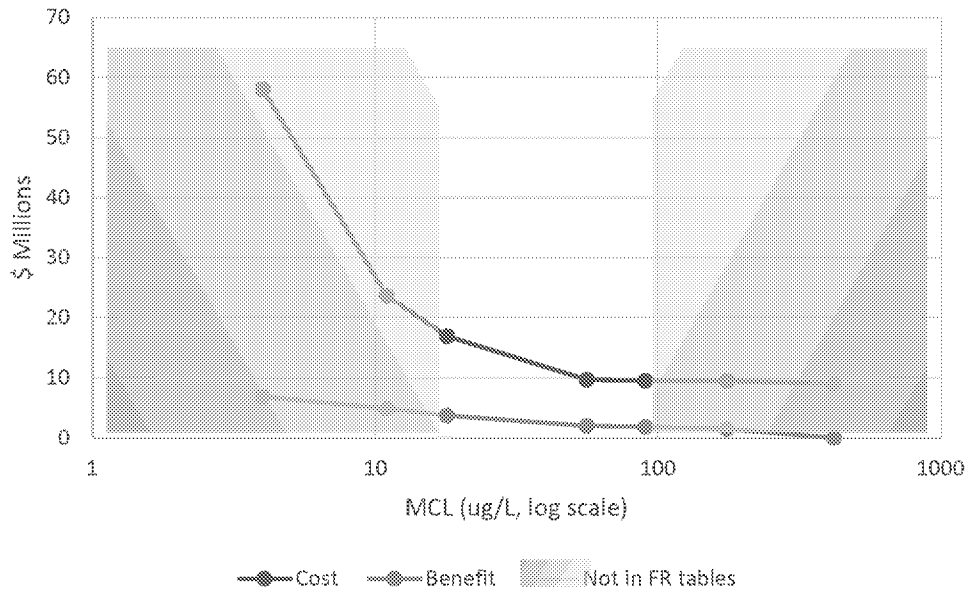
APPENDIX

Comparison of Annual Costs and Benefits by MCL for the Proposed Standardized Monitoring Framework (Millions; 2017$)

MCL	Cost 3% Discount	Benefit 3% Discount[a]	Cost 7% Discount	Benefit 7% Discount[a]
4 µg/L	$58.11	$6.85 ($1.50-$12.20)	$61.84	$1.15 ($0.25-$2.04)
11 µg/L	$23.64	$4.85 ($1.06-$8.64)	$24.89	$0.81 ($0.18-$1.45)
18 µg/L[b]	$16.95	$3.68 ($0.80-$6.56)	$17.96	$0.62 ($0.14 -$1.11)
56 µg/L[c]	$9.67	$2.00 ($0.44 -$3.57)	$10.28	$0.34 ($0.07- $0.60)
90 µg/L[b]	$9.51	$1.83 ($0.40-$3.26)	$10.10	$0.31 ($0.07-$0.55)
175 µg/L	$9.44	$1.48 ($0.32-$2.63)	$10.02	$0.25 ($0.05-$0.44)
420 µg/L[d]	$9.02	$0.00 ($0.00-$0.00)	$9.58	$0.00 ($0.00-$0.00)

Notes:
a. The benefit values are based upon avoided future income loss to the children who do not experience IQ decrements and discount rates have a significant effect on their magnitude.
b. EPA took comment on alternative MCLG/MCL of 18 and 90 µg/L.
c. EPA proposed an MCL of 56 µg/L
d. The highest perchlorate concentration observed in UCMR 1 is one sample at 420 ppb.

Chart for 3% Discount Rate Cost and Benefit Values



MCL (µg/L)	4	11	18	56	90	175	420
IQ loss	0.5	0.75	1	2	3	5	8.2

Message

From: Fotouhi, David [Fotouhi.David@epa.gov]
Sent: 5/14/2020 9:58:48 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
Subject: RE: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water
Attachments: perchlorate_reductions_5.14.20.pdf

We've looked at the issue regarding the "Reductions of Perchlorate in Drinking Water" document. If there is an ability to change the text to match the language of the proposal, we think that is the best course of action. Instead of saying "the EPA concludes that...," we should say "The information suggests that..." or "The information indicates that..." If there is no ability or willingness to make this change, let me know.

David Fotouhi

Principal Deputy General Counsel
Office of General Counsel
U.S. Environmental Protection Agency
Tel: +1 202.564.1976
mailto:fotouhi.david@epa.gov

From: Goerke, Ariadne <Goerke.Ariadne@epa.gov>
Sent: Thursday, May 14, 2020 4:35 PM
To: Fotouhi, David <Fotouhi.David@epa.gov>
Subject: FW: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

I just spoke with David Risley regarding his email below and he recommends that you reach out to Charlotte to help OW figure out what to do here. He said you were aware that they were getting questions that indicate a draft of the final rule has been leaked. Let me know if you want me to do something else. Thanks.

Ariadne Goerke
Acting Associate Deputy General Counsel
U.S. Environmental Protection Agency
202-564-5471 (office)
Ex. 6 Personal Privacy (PP)

From: Risley, David <mailto:Risley.David@epa.gov>
Sent: Thursday, May 14, 2020 4:13 PM
To: Goerke, Ariadne <mailto:Goerke.Ariadne@epa.gov>
Cc: Wadlington, Christina <mailto:Wadlington.Christina@epa.gov>
Subject: FW: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

Hey Ariadne,
We are seeking OGC's help on an potential issue. We posted https://www.epa.gov/sites/production/files/2020-05/documents/perchlorate_reductions_5.14.20.pdf on perchlorate today and it includes a statement at the end that EPA "concludes" that there is infrequent occurrence of perchlorate at the levels of public health concern.

We are concerned that the reporter and/or the public will interpret the document as a conclusory agency action on perchlorate. Christina (copied here) is pulling together language we can use to clarify what decisions the agency would have to make to take a final action on perchlorate. That information would help us demonstrate that this is not our final action on perchlorate.

We would appreciate OGC's review of this language. Thanks so much!

David Risley
EPA Office of Water Communications
Office 202-343-9177
Cell 202-731-3068

From: Wadlington, Christina <mailto:Wadlington.Christina@epa.gov>
Sent: Thursday, May 14, 2020 3:34 PM
To: Risley, David <mailto:Risley.David@epa.gov>
Subject: FW: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

As requested.

Summary: Based on this quote: "The EPA has compared this information to the lowest potential Maximum Contaminant Level Goal under consideration by the Agency in the June 19, 2019 proposal. The EPA concludes that there is infrequent occurrence of perchlorate at the levels of public health concern." (Note this is the conclusion found in: https://www.epa.gov/sites/production/files/2020-05/documents/perchlorate_reductions_5.14.20.pdf%E2%80%9D)

Requesting EPA to explain: What is the lowest potential mcl in the first sentence, and the conclusion that it has reached. What does EPA mean by the levels of public health concern? What levels are these? The lowest potential mcl or what? Can you please explain.

OGWDW Responses
Point 1. What is the lowest potential mclg in the first sentence.
The agency's June 2019 proposal includes a health-based Maximum Contaminant Level Goal (MCLG) of 56 micrograms per liter. In addition, the agency requested comment on three alternative options: 1) a MCLG for perchlorate set at 18 micrograms per liter, 2) A MCLG for perchlorate set at 90 micrograms per liter and, 3) Withdrawal of the agency's 2011 determination to regulate perchlorate in drinking water. https://www.epa.gov/sdwa/perchlorate-drinking-water

Point 2. and the conclusion that it has reached.
EPA concluded the levels of perchlorate in drinking water has decreased over time. The main factors contributing to the decrease in perchlorate levels include: the promulgation of drinking water regulations for perchlorate in California and Massachusetts; and remediation activities at perchlorate contaminated sites, particularly the ongoing remediation efforts in the state of Nevada to address perchlorate contamination in groundwater adjacent to the lower Colorado River upstream of Lake Mead.

Point 3. What does EPA mean by the levels of public health concern? What levels are these? The EPA is referring to the MCLGs from the proposed regulation.

From: Risley, David
Sent: Thursday, May 14, 2020 2:18 PM
To: Wadlington, Christina <mailto:Wadlington.Christina@epa.gov>
Subject: FW: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

Is this OK? Please feel free to edit/rewrite.

Question: What is the lowest potential mcl in the first sentence, and the conclusion that it has reached. What does EPA mean by the levels of public health concern? What levels are these? The lowest potential mcl or what? Can you please explain. Thank you, Amena

"The EPA has compared this information to the lowest potential Maximum Contaminant Level Goal under consideration by the Agency in the June 19, 2019 proposal. The EPA concludes that there is infrequent occurrence of perchlorate at the levels of public health concern."

Response: The agency's June 2019 proposal, proposed a Maximum Contaminant Level (MCL) and a health-based Maximum Contaminant Level Goal (MCLG) of 56 micrograms per liter. The proposal sought comment on alternatives, including 18 micrograms per liter as the lowest alternative MCL and MCLG. EPA identified 15 water systems located across 12 states with at least one reported result that was greater than 18ppb. Although systems are not required to take actions to reduce perchlorate in drinking water, the EPA found that perchlorate levels have been reduced in many of the systems. The status of each of these systems is described in https://www.epa.gov/sites/production/files/2020-05/documents/perchlorate_reductions_5.14.20.pdf.

Separately, using recommendations from the EPA's Science Advisory Board, EPA conducted an in-depth scientific review of the health effects of perchlorate in the proposal. The Agency's peer reviewed health effects analysis indicates that higher levels of perchlorate in drinking water are less impactful to health than previously understood. As a result, EPA estimates that very few water systems currently have perchlorate in drinking water at levels of health concern. [Can we provide a level from the proposal?]

David Risley
EPA Office of Water Communications
Office 202-343-9177
Cell Ex. 6 Personal Privacy (PP)

From: Woods, Andrea <mailto:Woods.Andrea@epa.gov>
Sent: Thursday, May 14, 2020 12:53 PM
To: Risley, David <mailto:Risley.David@epa.gov>; Drinkard, Andrea <mailto:Drinkard.Andrea@epa.gov>
Subject: FW: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

David - do you have more info for her?

From: Saiyid, Amena <mailto:asaiyid@bloombergindustry.com>
Sent: Thursday, May 14, 2020 12:51 PM
To: Press <mailto:Press@epa.gov>

Subject: RE: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

Dear all,
Could you also please clarify what EPA specifically means in these two sentences?

What is the lowest potential mcl in the first sentence, and the conclusion that it has reached. What does EPA mean by the levels of public health concern? What levels are these? The lowest potential mcl or what? Can you please explain. Thank you, Amena

"The EPA has compared this information to the lowest potential Maximum Contaminant Level Goal under consideration by the Agency in the June 19, 2019 proposal. The EPA concludes that there is infrequent occurrence of perchlorate at the levels of public health concern."
: : : : : : : : : : : : : : : : :

Amena H. Saiyid
Air & Water Reporter

Bloomberg Industry Group

D: 703 341- 3695
Ex. 6 Personal Privacy (PP)
mailto:asaiyid@bloombergindustry.com
Twitter: @amenasaiyid

From: Saiyid, Amena
Sent: Thursday, May 14, 2020 12:43 PM
To: Press <mailto:Press@epa.gov>
Subject: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water
Importance: High

Follow up question: I am not entirely sure what EPA is saying here? This is not a final drinking water standard. This is just a report showing what EPA has found regarding perchlorate in drinking water, right?

: : : : : : : : : : : : : : : : :

Amena H. Saiyid
Air & Water Reporter

Bloomberg Industry Group

D: 703 341- 3695
Ex. 6 Personal Privacy (PP)
mailto:asaiyid@bloombergindustry.com
Twitter: @amenasaiyid

From: EPA Press Office [mailto:press@epa.gov]
Sent: Thursday, May 14, 2020 12:33 PM
To: Saiyid, Amena <mailto:asaiyid@bloombergindustry.com>
Subject: EPA Notes Successes in Reducing Perchlorate in Drinking Water

Today, the U.S. Environmental Protection Agency (EPA) is releasing information on reductions of perchlorate in drinking water due to actions that its

EPA Notes Successes in Reducing Perchlorate in Drinking Water

WASHINGTON (May 14, 2020) – Today, the U.S. Environmental Protection Agency (EPA) is releasing information on reductions of perchlorate in drinking water due to actions that its partners and the agency have taken to mitigate this contaminant and protect public health. The agency is also providing information for drinking water utilities on perchlorate.
"Because of steps that EPA, states and public water systems have taken to identify, monitor and mitigate perchlorate, the levels have decreased in drinking water" said EPA Administrator Andrew Wheeler. "This success demonstrates that EPA and states are working together to lead the world in providing safe drinking water to all Americans."
Since EPA made a determination to regulate perchlorate in drinking water in 2011, meaningful reductions have occurred due to actions taken by EPA, states and public water systems. The main factors contributing to the decrease in perchlorate levels include:
• Improved procedures for storage and handling of hypochlorite solutions used as drinking water disinfectants.
• Remediation activities at 60 Superfund sites to address perchlorate.
• Drinking water regulations for perchlorate in Massachusetts and California.

• Federal and state remediation activities at perchlorate contaminated sites, particularly the ongoing remediation efforts in the state of Nevada to address perchlorate contamination in groundwater adjacent to the lower Colorado River upstream of Lake Mead.

EPA remains committed to continuing to work with states and public water systems and is providing information to water systems on addressing perchlorate in drinking water. For more information on the declining levels of perchlorate in drinking water and information for drinking water utilities:
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-r%2F&data=02%7C01%7CBertrand.Charlotte%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903299356819&sdata=VoZkT2Va2I2dUQW7ZPemmRTJH5KZmDH6g%2Bmp3sos3F4%3D&reserved=0.

Background

On June 26, 2019, EPA published the notice of proposed rulemaking seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. EPA is developing a final action that reflects comments received on the agency's proposal and will be issued this June. For more information about EPA's proposal, see
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-y%2F&data=02%7C01%7CBertrand.Charlotte%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903299356819&sdata=kt6C%2BcndOcaatHqyVj21x2alfUhNrbuV9mhCPj%2Bh59s%3D&reserved=0.

Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches, and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern U.S., and can be found as a byproduct in hypochlorite solutions used for treating drinking water and nitrate salts used to produce fertilizers, explosives, and other products.

https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-t%2F&data=02%7C01%7CBertrand.Charlotte%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903299356819&sdata=S%2FSlFIoCui%2FOfMv7NXzXehVbCXapjTopZpIkyHO95b8%3D&reserved=0
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U.S. Environmental Protection Agency
1200 Pennsylvania Avenue Northwest
Washington, D.C. 20004

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https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-tw-mditrky-alyjhlhdr-u%2F&data=02%7C01%7CBertrand.Charlotte%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903299356819&sdata=f9UXVFWIMTETjkErVh%2FWmzXiY6WxBLYpYfy5sGRpJJo%3D&reserved=0
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&reserved=0

Message

From: Burneson.Eric@epa.gov [Burneson.Eric@epa.gov]
Sent: 5/23/2019 9:42:11 AM
To: Eric Burneson Ex. 6 Personal Privacy (PP)
Subject: Fwd: Revised FRN 5/23/19
Attachments: NPDWR for the Proposed Perchlorate Rule 5-23-19 Ver 0.docx; ATT00001.htm; Redline 5-23-19 Ver0 Perchlorate FRN.docx; ATT00002.htm

Sent from my iPhone

Begin forwarded message:

From: "Hernandez-Quinones, Samuel" <Hernandez.Samuel@epa.gov>
Date: May 23, 2019 at 1:03:20 AM EDT
To: "Burneson, Eric" <Burneson.Eric@epa.gov>
Cc: "Christ, Lisa" <Christ.Lisa@epa.gov>, "Khera, Rajiv" <Khera.Rajiv@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Messier, Dawn" <Messier.Dawn@epa.gov>
Subject: Revised FRN 5/23/19

Hi Eric,
Attached is a clean version of the FRN which incorporates the edits that were offered to OMB earlier tonight. I am also providing here a Redline version that shows the edits the we have incorporated (mainly format) since we sent an updated Version to OMB at 12:53 pm on 5/22/19.

Let me know if you have any comment on the attached files.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Burneson.Eric@epa.gov [Burneson.Eric@epa.gov]
Sent: 4/4/2019 11:34:45 PM
To: Nickerson, William [Nickerson.William@epa.gov]
Subject: Fwd: Revised Perchlorate FRN
Attachments: Perchlorate Proposed NPDWR Redline 4-4-19.docx; ATT00001.htm

FYI on our status. See below

Sent from my iPhone

Begin forwarded message:

> **From:** "Burneson, Eric" <Burneson.Eric@epa.gov>
> **Date:** April 4, 2019 at 6:21:17 PM EDT
> **To:** "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Guilaran, Yu-Ting" <Guilaran.Yu-Ting@epa.gov>
> **Cc:** "'Joe Tiago (Tiago.Joseph@epa.gov)'" <Tiago.Joseph@epa.gov>, "Hernandez-Quinones, Samuel" <hernandez.samuel@epa.gov>, "Khera, Rajiv" <Khera.Rajiv@epa.gov>, "Christ, Lisa" <Christ.Lisa@epa.gov>, "Messier, Dawn" <Messier.Dawn@epa.gov>, "Wehling, Carrie" <Wehling.Carrie@epa.gov>
> **Subject: RE: Revised Perchlorate FRN**
>
> Jennifer: Because we have had issues transmitting multiple files, I am resending this redline document in case it did not come through in the last email.
> Eric
>
> **From:** Burneson, Eric
> **Sent:** Thursday, April 04, 2019 6:17 PM
> **To:** Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
> **Cc:** Joe Tiago (Tiago.Joseph@epa.gov) <Tiago.Joseph@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
> **Subject:** Revised Perchlorate FRN
>
> Jennifer:
> Attached for transmission to the OW IO are revised draft notices for a Proposed National Primary Drinking Water Regulation. The first attachment is a clean version of the revised document and the second is a redline document that shows the changes made since the last OW-IO review.
>
> The changes made to the document include:
>
> **Ex. 5 AC/AWP/DP**
>
> The attached materials incorporate the comments that we received from you and from OGC. OGC has concluded that the drafts they reviewed "meets the consent decree obligations." Please let us know if you have any questions or concerns with the attached documents.
>
> Eric Burneson, P.E.
> Director of Standards and Risk Management

Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Perchlorate in Drinking Water

Background

- 2005 EPA posts RfD of 0.0007 mg/kg/day for perchlorate on the IRIS database based on the recommendations of the NRC.
  - Point of departure for RfD based on No Observable Effect Level (NOEL) for inhibition of iodide uptake by the thyroid
  - 10x uncertainty factor to address sensitive life stages NRC identified fetus of the pregnant woman as the most sensitive life stage, but also identified infants and developing children as other sensitive populations.
- In February, 2011 EPA published a determination to regulate perchlorate in drinking water.
  - The regulatory determination was made based upon health reference levels derived from the RfD using *life stage specific* exposure factors for infants and developing children as well as occurrence data collected from EPA's first unregulated contaminant monitoring rule (UCMR1).
  - SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013).

Science Advisory Board Recommendations

- In 2012, EPA sought recommendations from SAB on how to derive a MCLG for perchlorate in accordance with SDWA
  - May 29, 2013 report recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling (PBPK)."
  - ". . . [t]his data-driven approach represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages than is possible with the default approach for deriving an MCLG."
- To address SAB recommendations, EPA and FDA scientist have been working collaboratively since 2013 to develop a Biologically Based Dose-Response model (PBPK model) to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate.

National Resource Defense Council Lawsuit

- February 18, 2016, NRDC filed a complaint in the U.S. District Court for the Southern District of N.Y. alleging that EPA failed to perform a nondiscretionary duty under SDWA (Section 1449(a)(2)) to propose and finalize a NPDWR for perchlorate.
- The NRDC seeks court-ordered proposal and final deadlines; we are currently in settlement discussion with them.
- Ex. 5 AC/AWP/DP
- Ex. 5 AC/AWP/DP

Peer Review Process

- The peer review follows the 2013 EPA *Conflict of Interest Review Process for Contractor-Managed Peer Reviews of EPA HISA and ISI* policy based on 2004 OMB *Final Information Quality Bulletin for Peer Review* under the Information Quality Act.
- The review process is structured so that a contractor will select recognized scientific experts in both PBPK, PBPK/PD and/or BBDR modeling, toxicology, environmental risk assessment and other relevant expertise, and identify a meeting venue and manage the review.
- The review process provides opportunity for public comment on: nominated peer reviewers, charge questions, the model and reports.
- The process provides adequate time for the panelists to review and consider the model and draft reports.
  - The contractor will provide panelists with the peer review charge, the documents to be reviewed, and a summary of the public comments submitted on the draft documents prior to the meeting.
  - We anticipates holding the two-day review panel meeting this winter at a publicly accessible location to allow for observation. We intend to allow for the public to make brief statements during the meeting.
- The process provides adequate time for the agency to incorporate panel recommendations into our work prior to taking further action.

Peer Review Schedule <include? Revise dates?>

Task	Completion Date (Duration)
FR Notice 1 Published (solicits peer review nominations)	**March 1, 2016**
FR Notice 2 Published (solicits additional peer review nominations to expand panel)	**May 21, 2016** (30 day nomination period)
FR Notice 3 Published (announces cmt period on interim list of candidates, BBDR model, model report, and MCLG report)	**July 28, 2016** (30 day cmt period on interim candidate list) (60 day cmt period on model, model report, and MCLG report)
FR Notice 4 Published (announces final reviewers and pre-meeting arrangements)	**October 13, 2016**
Combined Panel Meeting Dates	**November 16 & 17, 2016**
Final Report	**January 19, 2017**
Revised Model and Report	**April 19, 2017** (3 months)

Peer Review Product
Biologically Based Dose Response Model

- The BBDR model was developed in collaboration with FDA scientists to predict the effect of perchlorate on the thyroid gland in lactating women, formula-fed and breast-fed infants
- The model predicts the effects of perchlorate on thyroid levels, specifically serum thyroid hormone concentrations (fT4), at different iodine nutrition levels and various levels of exposure to perchlorate
- The model report will describe the model development and how parameters were selected. It will also provide the effectiveness of the model when compared to available empirical data for fT4 levels, and will provide a dose-response evaluation and a sensitivity analysis.

Peer Review Product

Approaches for Use of the BBDR Model to Derive an MCLG for Perchlorate

- The BBDR model predicts fetal T4 (fT4) hormone levels, based on available data from third trimester pregnant women. This represents a source of model uncertainty, since the developing fetus is known to be more sensitive to thyroid hormone perturbation during the first trimester of development
- The modeled fT4 levels are then used to predict potential health impacts based on published data that demonstrates a relationship between changes in thyroid hormone levels and neurodevelopmental effects during the first trimester of development.
- Two endpoints are being evaluated through this modeling effort:
  - The percent change in Bayley Scales of Infant and Toddler Development [the Psychomotor Development Index (PDI)/Mental Development Index (MDI)] scores at various doses of perchlorate
  - The shift in the percentage of pregnant women and infant populations with hypothyroxinemia upon exposure to perchlorate as determined by BBDR model output.

Anticipated Stakeholder Reaction

- Some stakeholders may be critical of the highly technical, underlying science to model perchlorate in sensitive lifestages and the application of the model output to inform the MCLG.
- Industry groups (Perchlorate Study Group, American Chemistry Council); drinking water utilities, the U.S. Chamber of Commerce and the Department of Defense will likely be critical of the application of the BBDR model in sensitive iodide deficient populations to yield low potential values.
  - They will likely suggest that the BBDR model is based on a precursor effect, and may suggest the literature demonstrates that this precursor effect can be mitigated through sufficient intake of iodide.
  - They will likely also express concern with the expedited schedule for the peer review that resulted from the modified rule making schedule.
- Environmental groups may be critical of the approach to addressing the underlying science.
- Consumers, both those using public water systems and private wells, will likely be concerned about potential health risks from perchlorate.

Appointment

From: Owscheduling [Owscheduling@epa.gov]
Sent: 2/8/2019 8:15:39 PM
To: Owscheduling [Owscheduling@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Wildeman, Anna [wildeman.anna@epa.gov]; Newberry, Debbie [Newberry.Debbie@epa.gov]; McLain, Jennifer L. [Mclain.Jennifer@epa.gov]; McDonough, Owen [mcdonough.owen@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Mason, Paula [Mason.Paula@epa.gov]; Best-Wong, Benita [Best-Wong.Benita@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]; Penman, Crystal [Penman.Crystal@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; Ross, David P [ross.davidp@epa.gov]; Mejias, Melissa [mejias.melissa@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Bergman, Ronald [Bergman.Ronald@epa.gov]; Travers, David [Travers.David@epa.gov]; Thompkins, Anita [Thompkins.Anita@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Spraul, Greg [Spraul.Greg@epa.gov]; Fuld, John [Fuld.John@epa.gov]; Kramer, Jessica L. [kramer.jessical@epa.gov]
CC: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Risley, David [Risley.David@epa.gov]

Subject: Bi-Weekly w/OGWDW
Attachments: Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Brownbag -Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Untitled Attachment; Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Bi-Weekly w/OGWDW ; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Bi-Weekly w/OGWDW ; Untitled Attachment; Untitled Attachment
Location: Call in Ex. 6 Personal Privacy (PP)

Start: 9/10/2020 8:00:00 PM
End: 9/10/2020 8:45:00 PM
Show Time As: Busy

Recurrence: Weekly
every Thursday from 4:00 PM to 4:45 PM

Appointment

From: Owscheduling [Owscheduling@epa.gov]
Sent: 2/8/2019 8:15:39 PM
To: Owscheduling [Owscheduling@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Wildeman, Anna [wildeman.anna@epa.gov]; Newberry, Debbie [Newberry.Debbie@epa.gov]; McLain, Jennifer L. [McLain.Jennifer@epa.gov]; McDonough, Owen [mcdonough.owen@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Mason, Paula [Mason.Paula@epa.gov]; Best-Wong, Benita [Best-Wong.Benita@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]; Penman, Crystal [Penman.Crystal@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; Ross, David P [ross.davidp@epa.gov]; Mejias, Melissa [mejias.melissa@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Bergman, Ronald [Bergman.Ronald@epa.gov]; Travers, David [Travers.David@epa.gov]; Thompkins, Anita [Thompkins.Anita@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Spraul, Greg [Spraul.Greg@epa.gov]; Fuld, John [Fuld.John@epa.gov]; Kramer, Jessica L. [kramer.jessical@epa.gov]
CC: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Risley, David [Risley.David@epa.gov]

Subject: Bi-Weekly w/OGWDW
Attachments: Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Brownbag -Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Untitled Attachment; Bi-Weekly w/OGWDW Call in 202-991-0477 passcode 1300632; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Bi-Weekly w/OGWDW ; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Bi-Weekly w/OGWDW ; Untitled Attachment; Untitled Attachment
Location: Call in Ex. 6 Personal Privacy (PP)

Start: 8/6/2020 8:00:00 PM
End: 8/6/2020 8:45:00 PM
Show Time As: Busy

Recurrence: Weekly
every Thursday from 4:00 PM to 4:45 PM

Appointment

From: Burneson, Eric [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2cacb9a8d49f49af80531e9e2ccb9018-eburneso]
Sent: 5/5/2020 1:08:58 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Lisa Christ [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]

Subject: Perchlorate Response to Comments
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-4-20.egb.docx
Location: Microsoft Teams Meeting

Start: 5/5/2020 6:00:00 PM
End: 5/5/2020 6:30:00 PM
Show Time As: Busy

I would like to discuss the comments I have provided thus far on the perchlorate RTC document and provide an opportunity for you to ask any questions about comments to date.

Join Microsoft Teams Meeting

+1 202-991-0477 United States, Washington DC (Toll)

Conference ID: Ex. 6 Personal Privacy (PP)

Local numbers | Reset PIN | Learn more about Teams | Meeting options

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Appointment

From: Owscheduling [Owscheduling@epa.gov]
Sent: 12/19/2019 3:23:30 PM
To: Owscheduling [Owscheduling@epa.gov]; Ross, David P [ross.davidp@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; Betts, Aaron [Betts.Aaron@epa.gov]; Nagle, Deborah [Nagle.Deborah@epa.gov]; Behl, Betsy [Behl.Betsy@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]; Wendelowski, Karyn [wendelowski.karyn@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]; Fotouhi, David [fotouhi.david@epa.gov]; Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Mutz, John (Fletcher) [mutz.john@epa.gov]; Mejias, Melissa [mejias.melissa@epa.gov]; Tovar, Katlyn [tovar.katlyn@epa.gov]

Subject: Perchlorate Option Selection
Attachments: Time Sensitive Meeting Request: Perchlorate Option Selection; Option Selection for Perchlorate 1-7-20 .docx
Location: 3219A WJCE

Start: 1/7/2020 4:00:00 PM
End: 1/7/2020 5:00:00 PM
Show Time As: Busy

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 9/11/2017 3:01:29 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]
Subject: Fwd: Perchlorate FRN Package: Communications Updates
Attachments: Perchlorate Peer Review Roll Out_09.11.17.docx; ATT00001.htm

I think it would be helpful to give our Federal partners a heads up. I don't want them feeling like we told them st the last second. It sounds like these will be public very quickly after we get word from OFA. They have cleared OPA.

Thanks,
Jennifer

Begin forwarded message:

> **From:** "Tricas, Marisa" <tricas.marisa@epa.gov>
> **Date:** September 11, 2017 at 8:50:32 AM CDT
> **To:** "Grevatt, Peter" <Grevatt.Peter@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>, "Rodgers-Jenkins, Crystal" <Rodgers-Jenkins.Crystal@epa.gov>
> **Cc:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>, "Flaharty, Stephanie" <Flaharty.Stephanie@epa.gov>, "Christ, Lisa" <Christ.Lisa@epa.gov>, "Huff, Lisa" <Huff.Lisa@epa.gov>
> **Subject: Perchlorate FRN Package: Communications Updates**
>
> Happy Monday!
>
> I spoke with Allison this morning and we are to prepare to make phone calls to stakeholders as necessary once Sandy and Steph hear back (hopefully ASAP) on public inspection (preinspection) which will occur the business day before posting the FRs. Please let me know if you have any other questions!
>
> Attached is the final perchlorate communications peer review roll-out plan with Allison's additions reflected for your records.
>
> Sincerely,
>
> Marisa Tricas
> Communications Specialist
> Office of Ground Water and Drinking Water
> United States Environmental Protection Agency
> 1200 Pennsylvania Avenue NW
> Washington, D.C. 20004
> Office: 202-564-2955
> Mobile: 202-770-5092
> Office: WJC East 2104D
> Website: https://www.epa.gov/ground-water-and-drinking-water
>
> ---
>
> **From:** Dennis, Allison
> **Sent:** Wednesday, September 6, 2017 3:41 PM
> **To:** Tricas, Marisa <tricas.marisa@epa.gov>
> **Subject:** RE: For Your Review: Mikes Edited Desk Statement + Updates on Perchlorate FRN Package

Instead of announcing this upon FR publication, can we instead announce in upon the FR pre-inspection notice going live (that is when the cat is out of the bag and media inquiries start to roll in).

From: Tricas, Marisa
Sent: Wednesday, September 06, 2017 3:33 PM
To: Dennis, Allison <Dennis.Allison@epa.gov>
Subject: FW: For Your Review: Mikes Edited Desk Statement + Updates on Perchlorate FRN Package

Please find changes to desk statement reflected below in blue.

> As part of EPA's commitment to ensuring the safety of America's drinking water, the agency is moving forward with the peer review process of scientific materials to inform decision making on perchlorate in drinking water. EPA is seeking public comment on the nominated peer reviewers, the draft charge questions, and the scientific materials the panel will review. After the peer review is complete, EPA will take the next appropriate steps under the Safe Drinking Water Act.

Sincerely,

Marisa Tricas
Communications Specialist
Office of Ground Water and Drinking Water
United States Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, D.C. 20004
Office: 202-564-2955
Mobile: 202-770-5092
Office: WJC East 2104D
Website: https://www.epa.gov/ground-water-and-drinking-water

From: Dennis, Allison
Sent: Wednesday, September 6, 2017 3:00 PM
To: Tricas, Marisa <tricas.marisa@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>
Subject: RE: Final Communications Roll-Out Plan

I met w/Mike on this ..a few changes- can we go with the following desk statement and rollout plan (see below). **Can you quickly review so that I can provide this to OPA by 4 today** ((Mike just signed the FRNs).

On the notification schedule- instead of giving regions 3 days notice of this action Mike thought it might be better to announce this at the WDD mtg tomorrow either in his remarks (which andrea is preparing) or Peter's. **Can you all decide who will mention it?**

Lastly- as far as what date to announce this, let's wait to see when it looks like the OFR will actually print the notice and have OPA weigh in.

Statement:

As part of EPA's commitment to ensuring the safety of America's drinking water, the agency is moving forward with the peer review process for addressing perchlorate in drinking water. EPA is seeking public comment on the nominated peer reviewers, the draft charge questions, and the materials the panel will review. After the peer review is complete, EPA will take the next appropriate steps under the Safe Drinking Water Act.

Notification Schedule:
-2 days

- <!--[if !supportLists]--><!--[endif]-->SRMD notification of federal partners (FDA, ATSDR, NIEHS, OMB)
- <!--[if !supportLists]--><!--[endif]-->OPA calls to federal agencies' communications (if desired)

Release Day

9:00 a.m	Begin head's up calls to stakeholder list below
10:00 a.m	Congressional heads up emails
12:00 p.m	Website goes live – Broader congressional notifications (emails with link to website).
1:00 p.m	OW notice sent via GovDelivery

From: Tricas, Marisa
Sent: Wednesday, September 06, 2017 12:39 PM
To: Drinkard, Andrea <Drinkard.Andrea@epa.gov>; Dennis, Allison <Dennis.Allison@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: Final Communications Roll-Out Plan

Hi Andrea and Allison,

Attached you will find the Final Communications Roll-Out Plan for the Perchlorate Peer Review.

Sincerely,

Marisa Tricas
Communications Specialist
Office of Ground Water and Drinking Water
United States Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, D.C. 20004
Office: 202-564-2955
Mobile: 202-770-5092
Office: WJC East 2104D
Website: https://www.epa.gov/ground-water-and-drinking-water

Perchlorate Peer Review
Communications Plan

PUBLICATION RELEASE DATE: September 11, 2017

ACTION: The agency is undertaking an independent, external panel peer review and announces the release of scientific materials for public comment that will Inform the Safe Drinking Water Act decision making on perchlorate. **KEY MESSAGES**

- Perchlorate – a chemical used in rocket propellants and other applications – may disrupt the normal function of the thyroid gland in both children and adults.
- EPA is currently determining the appropriate scientific approach for understanding the health impacts of exposure to perchlorate in drinking water.
- EPA is conducting a peer review of the draft scientific approach to provide advice to EPA on steps that will yield a highly credible scientific product that is supported by the scientific community.
- EPA will use this peer reviewed science to make future decisions on perchlorate under the Safe Drinking Water Act.
- The agency is releasing the interim list of peer review candidates, draft charge questions as well as a draft scientific report.
- The report provides information regarding how EPA intends to apply BBDR model to inform a quantitative understanding of potential adverse health effects associated with exposure to perchlorate in drinking water.
- The scientific analysis is precedent-setting, therefore EPA is conducting a transparent and rigorous expert peer review process.
- After the peer review is complete, EPA will take the next appropriate steps.

ANTICIPATED REACTION

There is likely to be considerable interest and response to EPA's release of peer review materials and the peer review process itself. Over the past several years, stakeholders have provided extensive comments on publically reviewable perchlorate materials and notices, met with EPA senior officials, managers and staff and have written the Administrator numerous letters.

EPA was sued by NRDC for the Agency's failure to issue proposed and final regulatory actions for perchlorate in accordance with the timelines provided in SDWA. The court approved consent decree established a schedule for completing the peer review process (10/18/17) and signature of a proposed (10/31/18) and final rule (12/19/19).

Stakeholders and the press are aware that EPA has been working to implement SAB recommendations and develop a BBDR model and scientific approach to inform decisions on perchlorate.

Stakeholder response will generally be critical of the highly technical, underlying science to model perchlorate in sensitive lifestages and the novel application of the model output to inform an understanding of the health impacts of exposure to perchlorate in drinking water.

- Industry groups (Perchlorate Study Group, American Chemistry Council); drinking water utilities, the U.S. Chamber of Commerce and the Department of Defense will likely be critical of the underlying science
- Environmental groups will likely be critical of the underlying science.
- Consumers, both those using public water systems and private wells, will be concerned about potential health risks from perchlorate.

Perchlorate Peer Review
Communications Plan

DESK STATEMENT

As part of EPA's commitment to ensuring the safety of America's drinking water, the agency is moving forward with the peer review process of scientific materials to inform decision making on perchlorate in drinking water. EPA is seeking public comment on the nominated peer reviewers, the draft charge questions, and the scientific materials the panel will review. After the peer review is complete, EPA will take the next appropriate steps under the Safe Drinking Water Act.

Background

On January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). This level was determined using a reference based dose response based on the recommendation of the National Research Council (NRC).

In 2011, EPA announced its decision (76 FR 7762) to regulate perchlorate under the Safe Drinking Water Act (SDWA). In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The MCLG is a non-enforceable goal defined under the SDWA as "the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." The MCLG is one of the considerations in developing the enforceable maximum contaminant level (MCL) for a regulated contaminant. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

In response to the Science Advisory Board's recommendations, the Office of Water worked with scientists from the Office of Research and Development and the Food and Drug Administration to develop a biologically based dose-response (BBDR) model that accounts for population differences in iodide exposure and predicts changes in thyroid hormone levels that result from exposure to perchlorate. We also assessed epidemiology studies that link thyroid hormone changes to developmental effects. EPA completeda peer review of the BBDR model and the report provided by the reviewers can be found on EPA's website at:
https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water.

Legal Deadlines: On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

COMMUNICATIONS MATERIALS

Webpage (link will appear on https://www.epa.gov/dwstandardsregulations/perchlorate) will include:

Perchlorate Peer Review
Communications Plan

- Link to public inspection FR notice
- Draft Charge Questions
- Interim List of Peer Reviewers
- Draft scientific report on the application of the model to inform decisions on perchlorate

RELEASE SCHEDULE

-2 days

- SRMD notification of federal partners
- OPA calls to federal agencies' communications

Release Day (when publically available on FR site)

9:00 a.m	Begin head's up calls to stakeholder list below
10:00 a.m	Congressional heads up emails
12:00 p.m	Website goes live – Broader congressional notifications (emails with link to website).
1:00 p.m	OW notice sent via GovDelivery

STAKEHOLDER NOTIFICATION

OGWDW:

- Michael Deane, Director, National Association of Water Companies
- Tracy Mehan, Government Affairs Director, American Water Works Association
- Mike Paque, Executive Director, Groundwater Protection Council
- Alan Roberson, Executive Director, Association of State Drinking Water Administrators
- Lynn Thorp, National Campaigns Director, Clean Water Action
- Diane Van de Hei, Executive Director, Association of Metropolitan Water Agencies
- Sam Wade, Executive Director, National Rural Water Association
- Nathan Ohle, Executive Director, Rural Community Assistance Partnership
- Tom Neltner, Chemicals Policy Director, Environmental Defense Fund
- Alexandra Dapolito Dunn, The Environmental Council of States

OGC:

- Eric Olson/Mae Wu, Natural Resources Defense Council

OLEM (OSRTI):

- Association of State and Territorial Solid Waste Management Officials

Federal

- US Food and Drug Administration
- Agency for Toxic Substances and Disease Registry
- National Institute for Environmental Health Sciences
- Office of Management and Budget
- National Aeronautics and Space Administration
- Department of Defense

Perchlorate Peer Review
Communications Plan

EXTERNAL QUESTIONS AND ANSWERS

CONSUMER QUESTIONS

Where is perchlorate found?
Perchlorate occurs naturally in arid states in the Southwest United States, in nitrate fertilizer deposits in Chile, and in potash ore in the United States and Canada. It also forms naturally in the atmosphere. Perchlorate is manufactured and used as an industrial chemical and can be found in rocket propellant, explosives, fireworks and road flares. It has been found in some public drinking water systems and in food.

Why is perchlorate in drinking water a health concern?
Perchlorate may disrupt the normal function of the thyroid gland in both children and adults. In adults, the thyroid plays an important role in metabolism, making and storing hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. In fetuses and infants, thyroid hormones are critical for normal growth and development of the central nervous system. Perchlorate can interfere with the human body's ability to absorb iodine into the thyroid gland which is a critical element in the production of thyroid hormones.

How does perchlorate get into my drinking water?
Perchlorate is dissolves easily, is relatively stable and is mobile in water. While it has often been detected in water supplies in close proximity to sites where solid rocket fuel is manufactured or used, there are also many locations in the United States lacking a clearly defined source.

Besides drinking water, how else can people be exposed to perchlorate?
People are exposed to perchlorate primarily through eating contaminated food or drinking water. The Food and Drug Administration (FDA) Total Diet Study combines nationwide sampling and analysis of hundreds of food items along with national surveys of food intake to develop comprehensive dietary exposure estimates for a variety of demographic groups in the U.S. In the 2008-2012 survey the FDA found detectable levels of perchlorate in 97 percent of the foods sampled. The complete set of FDA perchlorate data can be found here:
[HYPERLINK "https://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077615.htm"]

Have public drinking water systems been sampled for perchlorate?
Customers served by a public water system can contact their local water supplier and ask if they test for perchlorate. If so, they are encouraged to obtain a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those tested by EPA, and whether the system meets state standards or guidelines. If you are concerned about the possibility of perchlorate in your drinking water and you are served by a private well, EPA recommends testing your drinking water. In addition, EPA recommends that residents reach out to their local public health department for more information on testing your water.

The most recent Consumer Confidence Report can be obtained from your drinking water utility, by visiting their website or contacting them for a copy. Some public water systems upload their Consumer

Confidence Report to EPA's website at: [HYPERLINK "http://www.epa.gov/ccr" \h]. Information about private wells can be found here: [HYPERLINK "http://www.epa.gov/privatewells" \h].

Also, if your public water system participated in collecting monitoring data for UCMR 1, you can find information about your system at: [HYPERLINK "https://www.epa.gov/dwucmr/first-unregulated-contaminant-monitoring-rule"].

I live in a community with elevated perchlorate levels. Who do I call to get more information about what my utility is doing to address the elevated levels?
Contact your local water supplier to find out more about perchlorate in your drinking water. If you don't know who your local water supplier is, the information should be included in your latest water bill.

I get my tap water from a private well. How can I find out if perchlorate are in my water?
If you are concerned about the possibility of perchlorate in your drinking water and you are served by a private well, EPA recommends testing your drinking water. Approved laboratories can analyze a sample of your water to determine whether perchlorates are present and at what concentrations. Your local water or health department or drinking water system should know if there is such a program in your area. In addition, EPA recommends that residents reach out to their local public health department or state who may be able to help provide support for testing or to seek such support from a responsible party. If no program has been established or support is not available in your area, you can pay to have independent testing done at a qualified testing lab (typical cost is several hundred dollars per sample).

More information about private wells can be found here: [HYPERLINK "http://www.epa.gov/privatewells" \h].

Can a person drink tap water containing perchlorate at or below the level of the health advisory every day of their life and not expect adverse health effects from these chemicals?
Yes, the EPA health advisory level offers a margin of protection for all Americans from adverse health effects for a lifetime of exposure to perchlorate in drinking water at 15ppb.

Can perchlorate be boiled out of my water?
No, perchlorate cannot be removed by heating or boiling water.

Should I be worried about reconstituting my child's infant formula with tap water?
Refer to FDA

Should I consider taking iodine dietary supplements if I am worried about perchlorate?
Refer to FDA

How does a utility reduce/remove perchlorate?
A number of options are available to drinking water systems to lower concentrations of perchlorate in the drinking water supply. In some cases, drinking water systems may be able to reduce concentrations of perchlorate by closing contaminated wells or changing rates of blending of water sources. Perchlorate can be removed using a number of advanced treatment techniques. Each technique has advantages and disadvantages depending on the level of perchlorate present in the source water, removal goals, other water quality parameters, competing treatment objectives, and treatment waste

disposal options. Regenerable and single-pass ion exchange, reverse osmosis, and fixed- and fluidized-bed biological treatment can all remove perchlorate from drinking water sources.

These treatment systems are used by some public water systems today, but should be carefully designed and maintained to ensure that they are effective for treating perchlorate.

Home drinking water treatment units are typically certified by independent third party organizations against ANSI (American National Standards Institute) standards to verify their contaminant removal claims. Some home filters remove impurities using reverse osmosis; however, there currently are no ANSI protocols for testing home treatment systems to verify that these devices effectively remove perchlorate or how frequently the filters should be changed in order to maintain removal efficiency.

Can I buy a home treatment device to remove perchlorate?
If you are concerned about perchlorate in your drinking water, you may consider purchasing a home treatment device such as a filter. However, in order to make a well-informed and cost-effective decision, consider checking with your water system or consumer confidence report to learn about the amount of total perchlorate in your water and identifying a device that has been independently certified to remove perchlorate.

[HYPERLINK "http://www.nsf.org/consumer-resources/what-is-nsf-certification/water-filters-treatment-certification/contaminant-reduction-claims-guide" \t "_blank"], the [HYPERLINK "https://www.wqa.org/" \t "_blank"], [HYPERLINK "http://ul.com/" \t "_blank"] and [HYPERLINK "http://www.csagroup.org/global/en/services/testing-and-certification" \t "_blank"] all certify home treatment products for removal of contaminants. The relevant perchlorate removal standard is [HYPERLINK "http://www.nsf.org/consumer-resources/health-and-safety-tips/water-quality-treatment-tips/standards-for-water-treatment-systems" \t "_blank"]. If you choose to use a home treatment device, it is very important to follow the manufacturer's operation and maintenance instructions carefully in order to make sure the device works properly.

Does perchlorate have a health advisory level?
Yes, on January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). For more information on the Interim Drinking Water Health Advisory for perchlorate can be found here: [HYPERLINK "http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.txt"]

Has a safe level of exposure for perchlorate been established?
On February 11, 2011, EPA determined that perchlorate meets the Safe Drinking Water Act criteria for regulation as a contaminant. The Agency found that perchlorate may have an adverse effect on the health of persons and is known to occur in public drinking water systems with a frequency and at levels that present a public health concern. Since that time, EPA has been reviewing the best available scientific data on a range of issues related to perchlorate in drinking water including its occurrence, treatment technologies, analytical methods and the costs and benefits of potential standards.

There also have been state actions on perchlorate standards, guidelines, and advisories. In 2006, Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L, and in 2007, California promulgated a standard of 6 µg/L. Twelve other states have established non-enforceable guidance

levels, action or advisory levels. Depending on the state, a particular level may require a public water system to notify the public, serve as a screening tool for further action, or guide clean-up actions.

Customers that are served by a public water system can contact their local water supplier and ask for information on perchlorate in their drinking water, and are encouraged to request a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state and EPA drinking water standards.

PEER REVIEW QUESTIONS

Why is EPA conducting a peer review?
EPA will ask peer reviewers to comment on products that the agency will use to inform decision making on perchlorate under the Safe Drinking Water Act

EPA believes that peer review is an important component of the scientific process. The critical feedback, suggestions, and new ideas provided by the peer reviewers stimulate creative thought, strengthen the interpretation of the reviewed material, and confer credibility on the product. The peer review objective is to provide advice to EPA on steps that will yield a highly credible scientific product that is supported by the scientific community.

What products will be reviewed?
Peer reviewers will be asked to comment on the draft report entitled "Peer Review Draft: Proposed Approach to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water." Additionally, EPA is seeking public comments on the peer review charge and the interim list of expert peer review panel candidates.

Where can I find the review products?
All documents in the docket are listed on the [HYPERLINK "http://www.regulations.gov"] website under Docket ID Numbers EPA-HQ-OW-2016-0438 and EPA-HQ-OW-2016-0439.

Can I provide comments on the review products?
Yes. The public will have an opportunity to review and comment on the draft charge questions, the interim list of peer reviewers and the draft report describing application of the model to inform decision making on perchlorate in drinking water.

Additionally, we intend to allow for people to make brief statements during the meeting, and any Safe Drinking Water Act decisions on perchlorate will be subject to public notice and comment.

How long is the comment period?
EPA announced that it's seeking public comments on two separate sets of materials. The first set is the interim list of peer review candidates and the draft charge questions. People should send their comments to Versar, Inc. no later than 21 days after publication in the Federal Register.

A companion notice, also published on the same date, requests comments on the draft scientific report on application of the model to inform decision making on perchlorate. People should send their comments to the docket no later than 45 days after publication in the Federal Register.

Perchlorate Peer Review
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Will the review panelists see my comments or just EPA?
EPA will provide panelists a summary of the public comments submitted on the draft products.

When and where will EPA hold the meeting?
The meeting is projected to occur during in the late fall of 2017 (exact date to be determined). EPA will announce the meeting in the Federal Register at least 30 days in advance to provide the meeting date, location and registration information. EPA anticipates holding the two-day meeting in the Washington, DC metro area.

What will EPA do with the public comments and panel recommendations?
A peer review summary report will be developed that contains the full final comments and recommendations from the peer reviewers. EPA will make the final peer review report available to the public.

EPA will consider any public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the documents.

How will the contractor select the reviewers?
The contractor considered and screened all candidates against the selection criteria described in the March 1, 2016, and June 3, 2016, Federal Register notices (81 FR 10617 and 81 FR 35760, respectively) which included being free of any conflict of interest and being available to participate in-person in the peer review meeting.

Following the screening process, the list was narrowed to 12 candidates. EPA is now soliciting comments on the interim list of 12 candidates. Once the public comments on the interim list of candidates have been reviewed and considered, and the Science Integrity Official has been consulted, the final list of peer reviewers will be selected.

What happens next?
Once the public comments on the interim list of candidates have been reviewed and considered, the final list of peer reviewers will be selected.

What happens after the peer reviewers are selected?
Following the selection process, the peer reviewers will be tasked with evaluating and providing written comments on the draft products. Additionally, peer reviewers will be provided a summary of public comments and will be provided with the full set of public comments submitted during the draft document's public comment period.

When will EPA establish a national drinking water standard for perchlorate?
EPA will to consider public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the peer review products. After the peer review is complete, EPA will take the next appropriate steps.

Why is it taking so long for EPA to regulate perchlorate?
In 2011, EPA announced its decision to regulate perchlorate under the Safe Drinking Water Act (SDWA).

Perchlorate Peer Review
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In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The SAB released its final report on May 29, 2013 and recommended that EPA use a novel scientific modeling approach.

The agency, with contributions from Food and Drug Administration scientists, spent over three years to develop the model that predicts changes in thyroid hormone levels that result from exposure to perchlorate. We also assessed epidemiology studies that link thyroid hormone changes to developmental effects. EPA convened a peer review panel to provide recommendations on the model in January 2017 and revised the model considering the comments received in the peer review report submitted to the agency on March 29, 2017. EPA is now initiating the second stage of peer review on scientific materials to support decision making on perchlorate.

INTERNAL QUESTIONS AND ANSWERS

What is the status of the NRDC complaint

On February 18, 2016, the Natural Resource Defense Council filed a complaint in the United States District Court for the Southern District of N.Y. alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- if peer review not complete by 10/18/2017, filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

Will the peer review products present alternative MCLGs?

No, the documents will not present alternative MCLGs. The documents present various scientific approaches for understanding the potential health impacts from exposure to perchlorate in drinking water. However some experts can be expected to use the scientific methodologies described in the report to speculate how the Agency may derive an MCLG.

Will the methodologies that will be presented to the peer reviewers result in MCLGs that are in the range of MCLs set by California (6 µg/L) and Massachusetts (2 µg/L)?

We do not yet know. The draft analysis could result in values higher than currently used. However, the upcoming peer review of the scientific assessment is an important factor in our understanding of the science.

What is our evaluation of perchlorate occurrence data?

The UCMR 1 perchlorate dataset is the best available nationally representative data on perchlorate occurrence in public water systems. Analytical detections of perchlorate at or above the minimum reporting level (4 µg/L) were identified in about 4% (155 of 3,865) of these systems. EPA estimates that between 5.1 million to 16.6 million people served by the sampled systems could be exposed to perchlorate in drinking water. While perchlorate analytical detections are fairly numerous and widespread geographically, the UCMR 1 findings indicate that perchlorate occurs at relatively low levels: about 85% of analytical perchlorate detections are less than 13 µg/L and 42% are less than 6 µg/L.

However, commenters have pointed out limitations of UCMR 1 for estimating current occurrence. The minimum reporting level is 4 µg/L. Since UCMR 1 data has been collected 2 states have enacted perchlorate standards (CA & MA) and remediation activities or new sources of perchlorate may have impacted concentration levels in public water systems.

Are there any cross-office implications of promulgating a drinking water regulation?
Yes, a drinking water regulation for perchlorate would become the applicable or relevant and appropriate requirement (ARAR) and would replace the current preliminary remediation goal (PRG) for CERCLA sites (current PRG is based on the Interim Drinking Water Health Advisory level of 15 µg/L).

Is there an Environmental Justice/Equity component for the affected communities?
Each community faces unique challenges when addressing concerns related to environmental issues. Perchlorates in drinking water are related to localized sources of contamination often near where these produced have been manufactured or produced. Currently, if water sampling results confirm that drinking water contains perchlorate at individual or combined concentrations greater than 15 parts per billion, water systems should undertake additional sampling to assess the level, scope and localized source of contamination to inform next steps.

How will the RfD, or the interim health advisory, be used to inform the MCLG?
Based on SAB recommendations EPA does not intend to use the perchlorate RfD to inform derivation of an MCLG. The SAB stated that it, ". . . recognizes that this is a novel approach as compared to previous MCLG derivations that use the RfD and exposure factors. However, PBPK/PDIUI modeling provides a more rigorous tool to integrate the totality of information available on perchlorate, and this approach may better address different life stage susceptibilities to perchlorate than the default MCLG approach."

Message

From: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Sent: 6/15/2020 9:52:34 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Attachments: Perchlorate Action Memo 6-15-20. v2.docx; Transmittal Memo JM to DR 6-15-20.v2.docx; Perchlorate Action Memo 6-15-20 v1.mark-up.docx

Eric,

I made the correction to 6/17. Jennifer has the memos (attached). I've also attached my mark-up with edits to align with OW's preferences.

Getting closer... it's been a long run!
Steph

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, June 15, 2020 2:45 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Stephanie
Can you change the signature deadline to 6/17 (its currently 6/18) in the memo. OGC and DOJ need an extra day to file.
As soon as these are done please send to Jennifer.
Thanks
Eric

From: Burneson, Eric
Sent: Monday, June 15, 2020 1:01 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Stephanie
Attached are the updated memos. Can you please review and transmit the revised to Jennifer.
Also please advise what other materials are needed beyond the OGC concurrence?
Eric

From: Flaharty, Stephanie
Sent: Monday, June 15, 2020 10:57 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

I am awaiting updated memos for review, thanks!

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, June 15, 2020 10:55 AM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>

Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Sam and Stephanie:
Can you please advise me of the status of the transmittal /Action memos. We expect OMB clearance today and will need to move this package forward.
Are you awaiting my review of what Stephanie sent on Friday or is there more work to put together the FR signature package?

From: Flaharty, Stephanie
Sent: Friday, June 12, 2020 8:24 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

---

From: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Sent: Thursday, June 11, 2020 5:13 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>
Subject: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Importance: High

Steph: Please make sure that the program leads for Perchlorate Final Action start with these memos for the final action next week.

Sandy

From: Evalenko, Sandy
Sent: Thursday, May 21, 2020 4:46 PM
To: Nurse, Leanne <Nurse.Leanne@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>
Cc: Manibusan, Mary <manibusan.mary@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Subject: Action for OMB review: NPDWR: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Leanne: Here's the OMB Review package for the NPDWR: Perchlorate Final Action (SAN 5555; RIN 2040-AF28). Attached are the signed transmittal memo, draft Action memo, OGC concurrence, and the FRN for OMB review. If you have questions, please let us know.

Thanks,
Sandy

Sandy Evalenko
Water Policy Staff
Office of Water (4101M)
3226K WJC East
(202) 564-0264 telephone

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Thursday, May 21, 2020 4:22 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: FW: Charlotte - for review/signature - Perchlorate FRN to OP for Interagency Review
Importance: High

Hi! Here is the signed memo. Thanks for pulling it together for me, Charlotte

---

From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Thursday, May 21, 2020 3:10 PM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Ross, David P <ross.davidp@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>
Subject: Charlotte - for review/signature - Perchlorate FRN to OP for Interagency Review
Importance: High

Hi Charlotte,

Please see the electronic blue folder for the Notice of Final Action on Perchlorate to go to OP to be submitted to OMB for interagency review. I spoke with Dave and he has delegated package approval/transmittal memo signature to you. When you are ready to approve, please sign the transmittal memo (attachment 1). Please let me know if you find any edits to the memo or the package. Once signed, please send it back to me, and Sandy will move it to the next step.

- For attachment 1, your e-signature in PDF will look something like this:

SHARON HAMER

Digitally signed by SHARON HAMER
Date: 2020.03.12 17:21:45 -04'00'

Attachments

1. SIGN: Transmittal memo for your signature
2. Draft Perchlorate FRN to be sent to OMB
3. Draft Action Memo (will be kept in draft until time for final FRN signature).
4. OCG Concurrence emails – see below my signature block

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: **aguirre.janita@epa.gov**

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Thursday, May 21, 2020 12:04 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Request for Concurrence - Revised Perchlorate FRN

Sam,

Per our discussion, I have reviewed the redlined version of all of the changes to the FRN since the FAR version. I confirmed that all of OGC's comments on the FAR version have been sufficiently addressed – and only had a couple of minor additional edits – please see attached (my edits are marked with comment bubbles). With these edits, the FRN is ready to move forward. Thanks.

Pooja

Pooja S. Parikh
Attorney- Advisor
U.S. Environmental Protection Agency
Office of General Counsel, Water Law Office
Phone: 202 564-0839
Email: parikh.pooja@epa.gov

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Thursday, May 07, 2020 9:52 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Perchlorate FRN -- OGC concurs with comment

On behalf of the General Counsel, I am providing OGC's concurrence on the Federal Register Notice referenced in the email below, subject to the attached comments. I will be representing OGC at the FAR meeting. Please let me know if you have any questions or require additional information. Thank you.

Pooja

Pooja S. Parikh
Attorney- Advisor
U.S. Environmental Protection Agency
Office of General Counsel, Water Law Office
Phone: 202 564-0839
Email: parikh.pooja@epa.gov

MEMORANDUM

SUBJECT: *Federal Register* Notice of Final Action on Perchlorate

FROM: Jennifer L. McLain
Director, Office of Ground Water and Drinking Water

TO: David P. Ross
Assistant Administrator

Attached for your approval and transmittal to the Office of Policy for the Administrator's signature is a *Federal Register* (FR) notice titled: "Notice of Final Action on Perchlorate."

On February 11, 2011, the U.S. Environmental Protection Agency (EPA or Agency) published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), EPA published the proposed National Primary Drinking Water Regulation (NPDWR) for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. EPA received approximately 1,500 comments on the proposed rule. In the attached notice, EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available science.

I recommend that you approve and transmit the attached notice to the Office of Policy to expeditiously send the FR notice to the Administrator for signature. The deadline for signature is June 17, 2020, to enable the Department of Justice to file a motion to terminate the Consent Decree prior to the deadline for promulgating a final perchlorate NPDWR. If you need additional information, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

Message

From: Tricas, Marisa [tricas.marisa@epa.gov]
Sent: 9/11/2017 1:50:32 PM
To: Grevatt, Peter [Grevatt.Peter@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: Perchlorate FRN Package: Communications Updates
Attachments: Perchlorate Peer Review Roll Out_09.11.17.docx

Happy Monday!

I spoke with Allison this morning and we are to prepare to make phone calls to stakeholders as necessary once Sandy and Steph hear back (hopefully ASAP) on public inspection (preinspection) which will occur the business day before posting the FRs. Please let me know if you have any other questions!

Attached is the final perchlorate communications peer review roll-out plan with Allison's additions reflected for your records.

Sincerely,

Marisa Tricas
Communications Specialist
Office of Ground Water and Drinking Water
United States Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, D.C. 20004
Office: 202-564-2955
Mobile: 202-770-5092
Office: WJC East 2104D
Website: https://www.epa.gov/ground-water-and-drinking-water

From: Dennis, Allison
Sent: Wednesday, September 6, 2017 3:41 PM
To: Tricas, Marisa <tricas.marisa@epa.gov>
Subject: RE: For Your Review: Mikes Edited Desk Statement + Updates on Perchlorate FRN Package

Instead of announcing this upon FR publication, can we instead announce in upon the FR pre-inspection notice going live (that is when the cat is out of the bag and media inquiries start to roll in).

From: Tricas, Marisa
Sent: Wednesday, September 06, 2017 3:33 PM
To: Dennis, Allison <Dennis.Allison@epa.gov>
Subject: FW: For Your Review: Mikes Edited Desk Statement + Updates on Perchlorate FRN Package

Please find changes to desk statement reflected below in blue.

> As part of EPA's commitment to ensuring the safety of America's drinking water, the agency is moving forward with the peer review process of scientific materials to inform decision making on perchlorate in drinking water. EPA is seeking public comment on the nominated peer reviewers, the draft charge

questions, and the scientific materials the panel will review. After the peer review is complete, EPA will take the next appropriate steps under the Safe Drinking Water Act.

Sincerely,

Marisa Tricas
Communications Specialist
Office of Ground Water and Drinking Water
United States Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, D.C. 20004
Office: 202-564-2955
Mobile: 202-770-5092
Office: WJC East 2104D
Website: https://www.epa.gov/ground-water-and-drinking-water

From: Dennis, Allison
Sent: Wednesday, September 6, 2017 3:00 PM
To: Tricas, Marisa <tricas.marisa@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>
Subject: RE: Final Communications Roll-Out Plan

I met w/Mike on this ..a few changes- can we go with the following desk statement and rollout plan (see below). **Can you quickly review so that I can provide this to OPA by 4 today** ((Mike just signed the FRNs).

On the notification schedule- instead of giving regions 3 days notice of this action Mike thought it might be better to announce this at the WDD mtg tomorrow either in his remarks (which andrea is preparing) or Peter's. **Can you all decide who will mention it?**

Lastly- as far as what date to announce this, let's wait to see when it looks like the OFR will actually print the notice and have OPA weigh in.

Statement:
As part of EPA's commitment to ensuring the safety of America's drinking water, the agency is moving forward with the peer review process for addressing perchlorate in drinking water. EPA is seeking public comment on the nominated peer reviewers, the draft charge questions, and the materials the panel will review. After the peer review is complete, EPA will take the next appropriate steps under the Safe Drinking Water Act.

Notification Schedule:
-2 days

- SRMD notification of federal partners (FDA, ATSDR, NIEHS, OMB)
- OPA calls to federal agencies' communications (if desired)

Release Day

9:00 a.m	Begin head's up calls to stakeholder list below
10:00 a.m	Congressional heads up emails
12:00 p.m	Website goes live – Broader congressional notifications (emails with link to website).
1:00 p.m	OW notice sent via GovDelivery

From: Tricas, Marisa
Sent: Wednesday, September 06, 2017 12:39 PM
To: Drinkard, Andrea <Drinkard.Andrea@epa.gov>; Dennis, Allison <Dennis.Allison@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: Final Communications Roll-Out Plan

Hi Andrea and Allison,

Attached you will find the Final Communications Roll-Out Plan for the Perchlorate Peer Review.

Sincerely,

Marisa Tricas
Communications Specialist
Office of Ground Water and Drinking Water
United States Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, D.C. 20004
Office: 202-564-2955
Mobile: 202-770-5092
Office: WJC East 2104D
Website: https://www.epa.gov/ground-water-and-drinking-water

Appointment

From: Penman, Crystal [Penman.Crystal@epa.gov]
Sent: 3/27/2017 6:42:19 PM
To: Campbell, Ann [Campbell.Ann@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Travers, David [Travers.David@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Mason, Paula [Mason.Paula@epa.gov]; Thompkins, Anita [Thompkins.Anita@epa.gov]; Osegueda, Carlos [Osegueda.Carlos@epa.gov]; Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]

Subject: Bi -Weekly w/ OGWDW
Attachments: One_pager_Perchlorate in drinking water_fv_32217.doc; One_pager_LCR Revisions Action Information 3-22-17.doc; OIG response_32217_pcg.docx
Location: 3219A WJCE

Start: 3/28/2017 5:30:00 PM
End: 3/28/2017 6:15:00 PM
Show Time As: Tentative

Recurrence: Weekly
every 2 week(s) on Tuesday from 1:00 PM to 1:45 PM

Message

From: Grevatt, Peter [Grevatt.Peter@epa.gov]
Sent: 3/22/2017 9:58:33 PM
To: Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]
Subject: RE: For Review: Perchlorate one pager and peer review report
Attachments: 1 pager perchlorate in drinking waterdmm 3-22-17.doc

With edits. Need to accept changes in the final.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 4:51 PM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: For Review: Perchlorate one pager and peer review report
Importance: High

Peter,

As discussed earlier, Ann/Mike asked to have these 1-pagers ready on Perchlorate and LCR so Mike can forward to the OA team as briefings are scheduled. The attached is the one pager (recently updated with a few comments from OGC).

Additionally, Eric drafted an email (highlighted below) from you to Mike on the receipt of the final peer review report for the BBDR model. Note: The reason for the email is the recent receipt of the final peer review report. We plan on posting it to the docket and make it publicly available so that the public will be able to view the recommendations received on how to improve the model. Since we haven't indicated to Mike the peer report is complete and we're ready for posting, the email would serve this purpose and get his ok/feedback before we can move to Comms and post.

If the memo is suitable, I can move it to Ann. Thank you

Regards,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 1:56 PM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: RE: Perchlorate peer review report

Yvonne; Please see the draft note to Mike about perchlorate peer review. Also please find attached a draft one pager for the A.0. describing our activities. Please note the attached is still under review by OGC but I am sending to you and copying Dawn so that she can convey and comments/concerns to all once she has had a chance to review.

Mike:
Please find attached, a one page summary of our activities on perchlorate. The attached provides background information, identifies key issues and a timeline for moving forward. The attached highlights the recently completed

peer review of the biologically based dose response (BBDR) model for perchlorate and the planned peer review of methodologies to develop alternative MCLGs using the BBDR model.

Please note that we recently received the final peer review report for the BBDR model. We plan to post this peer review document to our docket so that the public will be able to view the recommendations we have received for how to improve the BBDR model. The peer reviewers identified a number of areas for improvement or modification of the existing model for predicting thyroid hormone level changes caused by perchlorate exposure. The peer reviewers recommended that the Agency develop a plan for further actions in order to maximize the benefit of any model revisions that are undertaken and to make decisions about priorities, timelines, and resources. Peer reviewers noted that models can always be improved, but the goal is to have a model that is fit for the intended purpose. The peer reviewers noted that the lack of a clear definition of that purpose for this model (i.e., how the model outputs would be used in developing the desired drinking water regulations) contributed to the difficulty they had in assessing whether the model was sufficiently good to apply.

We are working with our colleagues in ORD and FDA to implement many of the recommendations the peer reviewers made to the BBDR model. We believe that the purpose of the BBDR model will be more evident with the preparation of the MCLG Report that will describe alternative approaches for applying the BBDR model to develop potential perchlorate MCLGs. We hope to brief the Administrator's office on the perchlorate peer review process in April and intend to cover the recommendations from the first peer review and the draft MCLG report in April.

Please let us know if there is any more information you would like us to prepare in order inform the Administrator's office of these important activities.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 1:28 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Perchlorate peer review report

Eric,

Ann and I were on the same page. She thought an email note from Peter to Mike would suffice , including something on the findings and recommendations contained in the report.
I was just sending a heads up to Christina about the Desk Statement and holding it till we get an ok.

Can you or Lisa provide a draft of the email for Peter?

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 1:26 PM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate peer review report

I spoke with Jennifer about this and one idea we have is to mention posting the peer review report in the note that Ann/Mike will send to the A.O.
The draft one pager for perchlorate is under review by OGC since it references the Consent Decree.

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 11:56 AM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate peer review report

I don't recall specifically mentioning placing the peer review report in the docket to Mike. We of course have spoken about conducting the peer review, we just did not get into the specifics of putting the report into the docket.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 11:48 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Perchlorate peer review report

Eric,
Jennifer and I do not recall teeing up (at the bi-weekly or LCR meetings) the Perchlorate peer review report and placing it in the docket to Mike. Do you or Lisa remember doing so? Anything Please advise. I don't want to hold anything up on the comms side, but I also know Ann is going to ask if we did.

DESK STATEMENT

To ensure the safety of drinking water for all Americans, EPA is continuing the regulatory process for perchlorate in drinking water. In response to recommendations from our Science Advisory Board, the agency is developing two new analyses to inform selection of a health based goal (the Maximum Contaminant Level Goal or MCLG) for the regulation. The first new analysis is the development of a biologically based dose response (BBDR) model and the second analysis is the development of methodologies to derive a MCLG for the regulation using the BBDR model. The agency held a peer review of the first of two new analyses to ensure the agency's perchlorate regulatory decision-making is based on the best available science. EPA has received the peer review report, is reviewing the recommendations and will be taking actions to improve the BBDR model as appropriate. EPA plans to conduct a second peer review of the second analyses describes methodologies for deriving a MCLG for using the BBDR model. To find a copy of the report please visit:
https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN 2040-AF28, significant

Purpose: To improve the health protection from perchlorate into drinking water consumers from perchlorate.

Background: On February 11, 2011, EPA announced its decision to regulate perchlorate based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant. SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013) and finalize the regulations 18 months after proposal (can extend up to 9 months).

Stakeholder Involvement: EPA consulted with the National Drinking Water Advisory Council in 2012 on potential requirements of the perchlorate regulation. EPA has also met or corresponded with industry groups including the Perchlorate Study Group, American Chemistry Council, the American Water Works Association and the U.S. Chamber of Commerce. EPA was sued by the Natural Resources Defense Council in 2016 for the Agency's failure to issue proposed and final regulations for perchlorate in accordance with SDWA timelines.

Key Issues/Internal Review: The key issue for perchlorate is establishing the Maximum Contaminant Level Goal (MCLG[1]) which is defined in SDWA as the "level at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety." In early 2012, EPA the Agency sought recommendations from the EPA's Science Advisory Board on how to derive a MCLG for perchlorate in accordance with SDWA. The SAB recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling." In response to SAB recommendations, FDA and EPA scientists worked to develop models to relate perchlorate exposure to biological effects to infants, and other life stages. EPA completed an expert peer review of the models, and we are preparing for a second expert peer review of methodologies to apply the model to identify potential MCLGs for perchlorate. Once peer review of these analyses are completed, OW will brief the Administrator and seek input on the level at whichthat level the MCLG should be set and whether the Agency should proceed with a perchlorate rulemaking (EPA reads the SDWA to allow the Agency to withdraw the determination to regulate through a new round of notice and comment rulemaking). EPA could withdraw the determination to regulate by publishing a preliminary determination not to regulate for public comment and

Commented [DMM1]: Just in case the reader is unfamiliar with the SAB

Commented [DMM2]: ??How about "EPA reads the SDWA to allow the Agency to withdraw the determination to regulate through a new round of notice and comment rulemaking."

Commented [GP3R2]: I'm OK with the DMessier suggested edit

Legal Deadlines: EPA is under a consent decree with enforceable dates of October 31, 2018 for signature of a proposed MCLG and NPDWR action and a signature date of December 19, 2019 for the finale actionMCLG and NPDWR for perchlorate.

[1] Maximum Contaminant Level Goal (MCLG) is a non-enforceable public health goal. The enforceable standard, the Maximum Contaminant Level (MCL) The MCL is set as close to the MCLG as feasible using best available treatment technology and taking cost into consideration.

Timing: In order to complete necessary analyses for development of a proposed rule, including the Heath Risk Reduction Cost Analysis required by SDWA, we will need to initiate expert peer review of the approaches to derive an MCLG in mid May and complete the review in October 2017. We would like to brief the A.O. about peer review in April.

Message

From: Tucker, Nicole [Tucker.Nicole@epa.gov]
Sent: 9/8/2017 9:23:54 PM
To: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Albert, Ryan [Albert.Ryan@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Hautman, Dan [Hautman.Dan@epa.gov]; Carroll, Gregory [Carroll.Gregory@epa.gov]
Subject: Publication(s) received for review-week of September 5th-September 9th
Attachments: Cylindrospermopsin toxicity.zip; DBPS and stillbirths.zip; PBPK.zip; ToxCast.zip; AEP_AOP-perchlorate.zip; Headwater mining.zip

Hi Crystal,
It has been a busy week for manuscripts. OGWDW received six manuscripts for review and we will be reviewing **five** of the manuscripts received. The manuscripts and their supplemental material are grouped together in zip files and are attached. Below is more information about the manuscripts and the reviewers. Please let me know if you have any questions, concerns, or any issues accessing the files.
Hope you have a great weekend!
-Nicole Tucker

Title: Cylindrospermopsin toxicity in mice after a 90-day exposure by the oral route
Author(s): N. Chernoff, D.J. Hill, I. Chorus, D.L. Diggs, H. Huang, J.R. Lang, T-T. Le, J.E. Schmid, G.S. Travlos, E.M. Whitley, C.R. Wood
Purpose of study: To investigate the potential mammalian toxicity of the cyanobacterial toxin, cylindrospermopsin (CYN) by the oral route of exposure by drinking water.
Received from: Vanessa Emerson
OGWDW Reviewer: Hannah Holsinger
Meaningful OGWDW equities expected: Yes
Review comments requested by: September 19, 2017 (Hannah has already reviewed this manuscript and the version with her edits are included in the zip file and has been sent back to Vanessa Emerson, the OW POC for manuscripts)
Comments to be submitted to: Vanessa Emerson

Title: Exposure to disinfectant by-products and the risk of stillbirth in Massachusetts
Author(s): Zorimar Rivera-Núñez, J. Michael Wright, and Amy Meyer
Purpose of study: The study objective was to examine risk of stillbirths in relation to DBP exposures.
Received from: Vanessa Emerson
OGWDW Reviewer(s): Stig Regli and Nicole Tucker
Meaningful OGWDW equities expected: Yes
Review comments requested by: September 19, 2017
Comments to be submitted to: Vanessa Emerson

Title: Encouraging the Physiologically-Based Pharmacokinetic (PBPK) Modeling Community to Meet the Rigors of Regulatory Review
Author: Yu-Mei Tan, Rachel Worley, Jeremy A. Leonard, Jeffrey Fisher
Purpose of study: The review sought to identify key issues impeding the application of PBPK models by regulatory and non-regulatory federal agencies.
Received from: Vanessa Emerson
OGWDW Reviewer: Stig Regli for policy
Meaningful OGWDW equities expected: ----
Review comments requested by: September 19, 2017
Comments to be submitted to: Vanessa Emerson

Title: High-Throughput Screening of ToxCast Phase I Chemical Library for Sodium Iodide Symporter (NIS) Inhibitors

Author(s): Jun Wang, Daniel R. Hallinger, Ashley S. Murr, Angela R. Buckalew, Steven O. Simmons, Tammy E. Stoker, and Susan C. Laws.
Purpose of study: To describe a novel screening approach has been developed to rapidly identify chemicals that can inhibit the uptake of iodide by the thyroid and disrupt the synthesis of thyroid hormones.
Received from: Vanessa Emerson
OGWDW Reviewer(s): Iliriana Mushkolaj, Hannah Holsinger, Nicole Tucker
Meaningful OGWDW equities expected: ----
Review comments requested by: September 14th, 2017, due to OW POC September 19th, 2017
Comments to be submitted to: Ryan Albert

Title: The Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks facilitate the integration of human health and ecological endpoints for Cumulative Risk Assessment (CRA)
Author(s): David E. Hines, Stephen W. Edwards, Rory B. Conolly, and Annie M. Jarabek
Purpose of study: This manuscript discusses how the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks can be used to organize and evaluate exposure and dose response data across multiple species and endpoints. The authors present a case study using perchlorate.
Received from: Vanessa Emerson
OGWDW Reviewer(s): In process of finding reviewer
Meaningful OGWDW equities expected: Yes
Review comments requested by: September 21st, 2017
Comments to be submitted to: Vanessa Emerson

Title: Spatial Convergence in Major Dissolved Ion Concentrations and Implications of Headwater Mining for Downstream Water **Quality**
Author(s): Brent Johnson, Elizabeth Smith, Jerry W. Ackerman, Amy Newbold, Sue Dye, Robyn Polinsky, Eric Somerville, Chris Decker, Derek Little, Gregory J. Pond, and Ellen D'Amico
Purpose of study: The authors evaluated downstream trends in major dissolved solutes that result from mining activities by looking at watershed spatial patterns (mean concentrations and temporal variability vs. watershed area) and compared headwater values with those further downstream. They also evaluated different mining scenarios, either all headwaters intensively mined or all mostly unmined, and predicted the potential downstream change in water chemistry.
Received from: Vanessa Emerson
OGWDW Reviewer(s): None
Meaningful OGWDW equities expected: No
Review comments requested by: September 12th, 2017
Comments to be submitted to: Vanessa Emerson

Nicole Tucker
US Environmental Protection Agency
Office of Ground Water and Drinking Water
Standards and Risk Management Division
202-564-1946

The Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks facilitate the integration of human health and ecological endpoints for Cumulative Risk Assessment (CRA)

David E. Hines[1], Stephen W. Edwards[1], Rory B. Conolly[1], and Annie M. Jarabek[2]

Affiliations: [1]U.S. Environmental Protection Agency, ORD, NHEERL
[2]U.S. Environmental Protection Agency, ORD, NCEA

Disclaimer: *This article has been reviewed in accordance with EPA policy and approved for publication. The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not necessarily indicate recommendation or endorsement of use.*

Abstract

Cumulative risk assessment (CRA) methods promote the use of a conceptual site model (CSM) to apportion exposures and integrate risk from multiple stressors. While CSMs may encompass multiple species, evaluating endpoints across taxa can be challenging due to data availability and physiological differences among organisms. Adverse Outcome Pathways (AOPs) describe biological mechanisms leading to adverse outcomes (AOs) by assembling causal pathways with measurable intermediate steps termed key events (KEs), thereby providing a framework for integrating data across species. We used a case study focused on the perchlorate anion (ClO_4^-) to highlight the value of the AOP framework for cross-species data integration. Computational models and dose-response data were used to evaluate the effects of ClO_4^- in twelve species and revealed a dose-response concordance across KEs and taxa. The Aggregate Exposure Pathway (AEP) tracks stressors from sources to the exposures and serves as a complement to the AOP. We discuss how the combined AEP-AOP construct helps to maximize the use of existing data and advances CRA by 1) organizing toxicity and exposure data, 2) providing a mechanistic framework of KEs for integrating data across human health and ecological endpoints, and 3) highlighting data gaps and technical limitations.

ED_005043_00057844-00001

Key Words: Cumulative risk assessment, Adverse Outcome Pathway (AOP), Ecotoxicology, Human Health, Aggregate exposure

Acronyms: AEP, Aggregate Exposure Pathway; AO, Adverse Outcome; AOP, Adverse Outcome Pathway; ClO_4^-, perchlorate anion; CRA, Cumulative Risk Assessment; CSM, Conceptual Site Model; GEAE, Generic Ecological Assessment Endpoint; HPT, Hypothalamic-Pituitary-Thyroid; KE, Key Event; KER, Key Event Relationship; KES, Key Exposure State; KTR, Key Transitional Relationship; MIE, Molecular Initiating Event; NIS, sodium-Iodide Symporter; T3, triiodothyronine; T4, thyroxin; TH, Thyroid Hormone; TSE, Target Site Exposure; TSH, Thyroid Stimulating Hormone

1. Introduction

Researchers commonly evaluate risk from chemical stressors in the context of a single substance and target organism (Moretto et al. 2017). However, organisms are simultaneously exposed to multiple environmental contaminants and non-chemical stressors, and understanding how these factors interact to affect the health of individuals and populations is often relevant (Lentz et al. 2015, Ankley et al. 2016). Growing concerns about the effects of multiple stressors led the United States Environmental Protection Agency (EPA) to develop a framework for cumulative risk assessment (CRA) to assess risk from the combined effects multiple chemical and non-chemical factors (EPA 2003). CRA methods, which can be qualitative or quantitative (Callahan and Sexton 2007), evaluate the effects of aggregated exposure from multiple sources on multiple endpoints to characterize risk for adverse outcomes (AOs; NRC 2009, Sexton 2012). These techniques promote the use of a conceptual site model (CSM) to account for the stressors in a given environment, and thus can facilitate place-based assessments by incorporating relevant exposure data for that location (Levy 2008).

While the emphasis of a CRA framework is on the effects of multiple chemicals and stressors (EPA 2003), the NRC (2009) report "Science and Decisions" highlighted the importance of considering

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"human health or ecological effects, taking account of such factors as vulnerability and background exposures", and the recent National Academies report (NASEM 2017) on the use of new technologies for decision support emphasizes the same for both data integration and to ensure comprehensive risk characterization corresponding to real-world scenarios. In contrast, traditional risk assessment approaches usually focus on a single target organism because confounding factors such as physiological differences among species may lead to a diversity of species-specific endpoints and relevant exposure concentrations. Furthermore, challenges both within and among species such as differences between field and laboratory studies or differences in experimental design that include exposure media, magnitude, and duration can complicate the integration of data from multiple organisms into risk assessments. Despite these challenges, however, integration of data across species remains essential for site-specific, place-based community risk assessments and the maturation of CRA (Meek et al. 2009).

In addition to variation in experimental design and measurement techniques across species, differences in the focus of human health and ecological endpoints can complicate multi-species data integration into CRA. Human health risk assessments typically focus on the occurrence of an adverse health effect at the level of the individual by identifying hazards, collecting and evaluating dose-response and exposure data, and combining this information to characterize risk (NRC 1983). For example, human health risk assessments may be concerned with risk of cancer from an environmental contaminant. Ecological risk assessments follow an analogous approach to human health risk assessments, but can focus on endpoints ranging from effects in individual organisms to community effects that can impact ecosystem services (Suter 2007, Paustenbach 2015). Guidance for these endpoints is provided in a report on Generic Ecological Assessment Endpoints (GEAEs) for ecological risk assessment (Barron and Suter 2016), which includes organism-level (e.g. survival or growth), population-level (e.g., abundance), ecosystem-level (e.g., production), and ecosystem service-level (e.g. waste treatment) responses. These challenges are well recognized in the problem formulation process within

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ecological risk assessment (Reinert et al. 1998), and advances in modeling frameworks and computational tools have enabled researchers to begin to address them.

In recent years, CRA frameworks have been developed to address the challenge of cross-species data integration. For example, multi-criteria decision analysis and combined exposures decision trees (Kiker et al., 2005; Price et al. 2012) are frameworks specifically designed to facilitate the evaluation of risk in both human health and ecological endpoints by summing hazard indices for endpoints in human and non-human species to estimate overall risk. However, a mechanism-based framework for organizing and integrating data to evaluate relative risk across multiple species remains to be developed. This work begins to address this challenge by combining the Adverse Outcome Pathway (AOP; Ankley et al. 2010, Villeneuve et al. 2014a) and Aggregate Exposure Pathway (AEP; Teeguarden et al. 2016) frameworks to integrate dose-response data across multiple endpoints in multiple taxa.

AOPs describe biological pathways that link perturbations at the molecular level (molecular initiating events; MIEs) to AOs through a series of causal key events (KEs; Ankley et al. 2010). These KEs can be measured and used to confirm the activation of an AOP. AOs can occur at both the organismal and population levels (Kramer et al. 2011, Villeneuve et al. 2014b), making AOPs useful for integrating data across multiple species. Furthermore, AOPs are chemical-agnostic and pertain to any stressor(s) that activate a KE in the pathway (Villeneuve et al. 2014a, Edwards et al. 2016), therefore these constructs can form networks that encompass multiple chemicals and endpoints. AOP networks provide an organizing framework for toxicity data that describe responses after exposure to contaminants, but do not address the mechanisms of environmental fate and transport leading to these exposures.

The AEP framework parallels the AOP framework, but tracks contaminants from sources, through the environment, to target site exposures (TSEs) in affected organisms (Teeguarden et al. 2016). Ideally, the TSE will correspond to the same level of biological organization as the MIE, thereby allowing

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98 prediction of the expected perturbation of the AOP based on in silico or *in vitro* dose-response
99 information. This framework builds off previous ideas about the importance of incorporating multiple
100 routes of exposure into CRA (Wilkinson et al. 2000, Robson and Toscano 2007, NRC 2009, Sexton and
101 Linder 2011) by creating a generic CSM that is not constrained to a single site. The AEP consists of two
102 entities: a key exposure state (KES) that describes the amount of a stressor at a given location and time,
103 and a key transitional relationship (KTR) that describes either the transport of that stressor to a different
104 location or the transformation of that stressor into a different molecule. Individual AEPs can be
105 assembled into AEP networks to characterize the movement of multiple stressors and transformations
106 from one stressor to another (Teeguarden et al. 2016).

107 As with the AOP, these AEP networks are useful for CRA because they can organize exposure
108 data from multiple sources, make that information readily available for the development of site-specific
109 CSMs, and highlight data gaps at study locations. Furthermore, the description of the pathways leading
110 to TSEs in AEPs can include information on multiple organisms, making these constructs useful for
111 simultaneously considering exposure in humans and non-human species. The TSEs that serve as the
112 terminal nodes in AEP networks act as the inputs to AOP networks, thus these organizing frameworks
113 can be linked to form a joint AEP-AOP construct that describes a source-to-outcome representation of
114 risk for multiple AOs from multiple exposure pathways (Teeguarden et al. 2016, Escher et al. 2017).

115 The joint AEP-AOP construct can provide a mechanistic scaffold for organizing and integrating
116 exposure and toxicity data from multiple species (Norton and Schofield 2017). This construct has the
117 potential to be applied to CRA across classes of environmental contaminants affecting the same MIE
118 (Lumen and George 2017, Willemin and Lumen 2017, Clewell, R., in prep), as well as across species
119 affected by the same MIE. Cross-species AOP networks provide a common ground for evaluating
120 species-specific responses to environmental stressors across taxa by highlighting the effects of stressors
121 at the same KEs in different species. In this work, we develop techniques to apply the joint AEP-AOP

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construct to integrate human health and ecological data. We conduct a case study using a single contaminant, the perchlorate anion (ClO_4^-), to provide a simple example of this approach. We then discuss the potential of the AEP-AOP construct to advance CRA by enabling evaluation of risk from aggregate exposures across multiple species and endpoints.

2. Methods:

2.1 Case study

The ClO_4^- anion was selected for the case study presented in this work because it is a wide-spread environmental contaminant that has been heavily studied in several taxa (EPA 2002, NRC 2005). This contaminant is found in parts per billion (ppb) concentrations in sources ranging from drinking water, to soil, to plant material, to cow's milk (Leung et al. 2010), and can reach concentrations over 100 parts per million (ppm) in surface water at point locations (EPA 2002). Crucially, this chemical affects organisms primarily through a well-defined mechanism involving the competitive inhibition of iodide uptake into the thyroid at the sodium-iodide symporter (NIS; Carrasco 1993, Eskandari et al. 1997, EPA 2002, NRC 2009, Sijimol et al. 2015). NIS inhibition affects the hypothalamic-pituitary-thyroid (HPT) axis by decreasing iodide availability in the thyroid gland, resulting in decreased thyroxin (T4) and triiodothyronine (T3) synthesis. Reductions in these thyroid hormone (TH) levels can result in a feedback response of increases in thyroid stimulating hormone (TSH) production in the pituitary gland, and can have important effects on the growth and development of organisms (Figure 1; de Groef et al. 2016). Conservation of HPT axis biology, and therefore pieces of the NIS inhibition AOP, across diverse taxa make ClO_4^- a straightforward compound for demonstrating proof of concept and developing techniques for cross-species data integration using a joint AEP-AOP construct.

We assembled dose-response data for ClO_4^- exposure from twelve species, eight vertebrate and four invertebrate, to demonstrate the utility of the AEP-AOP construct for informing cross-species CRA.

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145 Among the vertebrate species, mammals were represented by humans, rats (*Rattus* sp.), meadow voles
146 (*Microtus* sp.), and rabbits (*Oryctolagus cuniculus*), while amphibians were represented by the African
147 clawed frog (*Xenopus laevis*), fishes were represented by zebrafish (*Danio rerio*) and mosquito fish
148 (*Gambusia holbrooki*), and birds were represented by the bobwhite quail (*Colinus virginianus*).
149 Invertebrate species examined in this study included earthworms (*Eisenia foetida*), mosquito larvae
150 (*Culex quinquefasciatus*), the water flea (*Daphnia magna*), and the sand dollar (*Peronella japonica*).
151 Although invertebrates lack an HPT axis, these organisms were included in this study because NIS
152 homologs, as well as adverse effects of ClO_4^- exposure, have been reported in invertebrates (Benvenga
153 et al. 1999, Sorensen et al. 2006). Furthermore, TH production has been suggested to occur in
154 invertebrates (Satio et al. 1998), thus a plausible basis exists for AOPs linking NIS inhibition to AOs in
155 these organisms. The organisms evaluated in this study included representative members from the
156 different taxa of animals examined in prior ecological risk assessments for ClO_4^- (EPA 2002, Smith et al.
157 2001, Theodarkis et al. 2006), and were selected based on the availability of dose-response data for KEs
158 in the NIS inhibition AOP. Furthermore, these species possessed different relevant exposure pathways,
159 physiology, life-history traits, and AOs, facilitating the demonstration of data integration in the presence
160 of these complicating factors.

161 We focused on endpoints contributing to four AOs among these species (Table 1).
162 Developmental neurotoxicity was selected as the AO to inform human health risk because NIS inhibition
163 can reduce maternal serum TH levels available to the fetus and passive transport of ClO_4^- across the
164 placental barrier an additionally affect TH production in the fetus, making this the most susceptible
165 human life stage and endpoint to exposure (NRC 2005, Yarrington and Pearce 2011, Suh et al. 2014).
166 We used findings from established assays such as the FETAX (Frog Embryo Teratogenesis Assay –
167 Xenopus) assay (Dawson and Bantle 1987), which relies on the link between THs and metamorphosis in
168 amphibians, to inform selection of AOs for non-human species. Data supporting developmental

169 neurotoxicity as a result of ClO_4^- exposure were also available for rats, the African clawed frog, and
170 zebrafish (EPA 2002, Goleman et al. 2002, Mukhi et al. 2007), therefore we considered this AO in these
171 species as well. Other AOs considered in this work were based on the reported effects of ClO_4^- in the
172 examined species and conformed to the guidelines for GEAEs presented in Barron and Suter (2016).
173 These GEAEs included altered growth in zebrafish, mosquito larvae, and water fleas, decreased survival
174 in mosquito fish, earthworms, and mosquito larvae, and decreased fecundity in zebrafish, meadow
175 voles, earthworms, and water fleas. Impaired metamorphosis was used as a measurement endpoint in
176 frogs and sand dollars, therefore we included these organism in the altered growth GEAE (Figure 1).
177 Data for specific AOs were not available for rabbits and quails, but these species were included in this
178 study because dose-response data for intermediate KEs in the NIS inhibition AOP were available.

179 2.2 Adverse Outcome Pathway (AOP) network

180 The AOP network portion of the AEP-AOP construct assembled the NIS inhibition AOPs of the
181 different species examined to provide a common ground for comparison. We based this network on the
182 preliminary AOP for NIS inhibition in mammals authored by Gilbert and colleagues in the AOPwiki (AOP
183 number 134; [HYPERLINK "https://aopwiki.org/"]) and the NRC (2005) assessment for ingested
184 perchlorate. NIS inhibition was the only MIE in this network, and led to decreased TH synthesis and
185 depletion of TH (T3 and T4) in the thyroid as an early biological effect for all of the vertebrate species
186 examined. We included a separate KE for depletion of TH in the thyroid as an early effect in the AOP
187 network because depleted stores of thyroid hormones in the colloid result in subsequent upregulation
188 of thyroid stimulating hormone (TSH), and data for this KE were available across the taxa examined.
189 Decreased serum TH levels result from these early biological effects in all species, and the branching of
190 subsequent KEs reflected the diversity of the AOPs across all of the species examined (Figure 1). For
191 example, altered hormone economy can result in hypertrophy and hyperplasia of the thyroid gland to
192 compensate. Deficits in TH ultimately lead to developmental neurotoxicity in humans (EPA 2002, NRC

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193 2005) assessed by brain morphometry and behavior, and to different AOs in other species such as
194 impaired metamorphosis (growth) in the African clawed frog (Goleman et al. 2002, Figure 1). Altered
195 structure and functions of thyroid tissues aside from colloid depletion were classified as "other thyroid
196 histology changes" (Figure 1), and included angiogenesis (Patiño et al. 2003), follicle cell hypertrophy
197 (Tietge et al. 2005), and hyperplasia (Bradford et al. 2005),. These other thyroid histology changes were
198 not directly linked to AOs or GEAEs because it is unclear if these changes are causal of downstream KEs
199 or if they are a response to systemic alterations, and AOs and GEAEs stemming from altered
200 development were used to categorize the different effects of NIS inhibition across species. The resulting
201 AOP network was used to organize dose-response data for endpoints pertaining to KEs and facilitate the
202 integration of this information to inform CRAs.

203 2.3 Aggregate Exposure Pathway network

204 The AEP network portion of the AEP-AOP construct represents the movement of the ClO_4^- anion
205 in the environment from its sources to different TSEs in the species examined. This places the measured
206 exposures used as input for the AOP network in a relevant context and could be used to relate the
207 current results to a site-specific risk assessment. Thus, the AEP network can serve as a general
208 representation of a conceptual site model (CSM; Teeguarden et al. 2016), as is highlighted by the generic
209 AEP network for ClO_4^- presented in this work.

210 The generic AEP network contained transport pathways for the ClO_4^- anion from multiple
211 sources (atmospheric deposition, water discharge, and disposal in the form of ClO_4^- salts) through
212 several different media including groundwater, surface water, and soil transportation (Figure 1). These
213 pathways include both direct exposure to organisms through contaminated media and exposure
214 through trophic interactions with organisms in intermediate KESs. Previous ecological assessments for
215 ClO_4^- have considered possible exposure to animals through accumulation of the ClO_4^- anion in the plant

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216 matter that they graze on (Smith et al. 2001, Smith et al. 2004). Therefore, we included consumption of
217 plant matter for both human and non-human species into the AEP. TSEs in the AEP are driven by
218 Absorption, Distribution, Metabolism, and Excretion (ADME) processes, which describe the amount of
219 ClO_4^- affecting the NIS inhibition MIE at the thyroid after external exposure in each organism (Figure 1).
220 In mammals, these processes are complicated by the fact that both ClO_4^- and maternal TH cross the
221 placenta into the fetus, thus adding additional ADME considerations. Species specific TSEs resulting
222 from ADME processes link the AEP network and the AOP network. Flows between KESs in the AEP were
223 not quantified for the purpose of this case study, as environmental exposure data were not necessary to
224 demonstrate cross-species integration of toxicity data and the generic AEP network does not represent a
225 specific, measurable location. However, the incorporation of the AEP network into the AEP-AOP
226 construct is crucial to illustrate how the techniques presented in this work can inform CRAs by creating a
227 context for considering relevant environmental exposures and by highlighting knowledge gaps in
228 relevant exposure mechanisms.

229 2.4 Data acquisition

230 Dose-response data for KEs in the NIS inhibition AOP network were obtained from literature
231 sources and included a combination of laboratory experiments and model outputs. For humans, the
232 point of departure (POD) of 7.0 µg/kg/d was obtained from Greer et al. (2002), which provided *in-vivo*
233 data for NIS inhibition from ClO_4^-, however no further human specific empirical data for NIS inhibition
234 were available. We used the biologically based dose-response (BBDR) model for a pregnant mother and
235 fetus presented in Lumen et al. (2013) to simulate ADME processes in humans and to estimate
236 hypothyroxinemia (decreased serum T4) as an early biological effect of NIS inhibition. This model
237 allowed for consideration of susceptible populations of interest by predicting serum free T4 levels in
238 both the mother and fetus at different levels of ClO_4^- and iodide intake. We considered the doses of
239 ClO_4^- necessary to induce predicted hypothyroxinemia in women receiving the FDA recommended 200

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240 μg iodide per day, as well as in iodide-deficient women receiving just 75 μg iodide per day, to provide
241 estimations across a range of relevant iodide intake conditions (Lumen et al. 2013). For KEs downstream
242 of serum T4 reduction, which were not included in the BBDR model, we hypothesized that a ClO_4^- dose
243 at least as high as the dose necessary to induce hypothyroxinemia would be required for activation. The
244 reference dose (RfD) for oral consumption of the ClO_4^- anion presented in the EPA Integrated Risk
245 Information System (0.7 μg/kg/d; EPA 2005, NRC 2005) was also included in this case study to provide a
246 context for dose-response data.

247 Data sources for non-human species were obtained through prescribed searches of the
248 ECOTOXicology knowledgebase (EPA 2016), as well as from the 2002 EPA toxicological review and risk
249 characterization for ClO_4^- (EPA 2002). ECOTOX search parameters for each species included an exact
250 match for genus and species name, "Perchlorates" as a predefined chemical group, and Lowest-
251 Observed-Effect-Concentration (LOEC), No-Observed-Effect-Concentration (NOEC), Lowest-Observed-
252 Effect-Level (LOEL), and No-Observed-Effect-Level (NOEL) as endpoints. No further search parameters
253 were provided and results were sorted by response site and organism life stage. The relevant data
254 identified through the ECOTOX search was added to the data included in the 2002 EPA review. The final
255 data set included NOEC, LOEC, NOEL, LOEL, benchmark dose modeling (BMD) values and the 95%
256 confidence limit of the BMD (BMDL) values.

257 2.5 Data integration

258 We used the AOP network as a framework to address the challenges of integrating toxicity data
259 across human health and ecological endpoints. This framework allowed for the organization of data
260 from different studies into aggregated KEs, each of which spanned multiple measured endpoints, to
261 create a context for comparison. We used the conceptual AOP network (Figure 1) to assemble a total of
262 nine aggregated KEs from twenty-nine different measurement endpoints (Table 1). Although data were

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263 not available for every KE in all species, each AOP in the AOP network shared the NIS inhibition MIE and
264 the early KEs of T4/T3 decrease, and TSH increase. When assembling data, we separated colloid
265 depletion from other thyroid histological changes to reflect the fact that colloid depletion must occur
266 before downstream KEs and AOs. The remaining four KEs considered in this study, which are AOs
267 (Table 1), had equal proximity to the MIE and were not assumed to occur sequentially.

268 Data generated by different experimental designs were adjusted to be consistent within and
269 across aggregated KEs. While doses for terrestrial organisms were often reported in units of μg/kg/d,
270 aquatic organisms are dosed by media concentration (μg/L or ppb). The dose metrics from all studies
271 were converted to μg/kg/d, and the blood concentration of ClO_4^- for aquatic organisms was assumed to
272 be equal to the media (water) concentration. This assumption is plausible in this case study due to the
273 high mobility of ClO_4^- (Liu et al. 2006) and equilibration of these organisms with their aqueous
274 environment, but tools such as physiologically based pharmacokinetic (PBPK) models may be necessary
275 to simulate ADME properties and estimate the internal dosimetry of other compounds.

276 We visually compared and evaluated data for the NOECs, LOECs, NOELs, LOELs, BMDs, and
277 BMDLs from different studies for each species and endpoint at each KE in the AOP network (Figure 2).
278 Data for lethal concentration (LC50) were also considered in the analysis, but were restricted to
279 invertebrates. We arrange the KEs in the NIS inhibition AOP network from the MIE to the AOs, then
280 plotted the ClO_4^- dose-response data (μg/kg/d) versus the KEs. This linearized arrangement of KEs
281 (Figure 2) does not imply causal relationships, but rather these relationships are described by AOP
282 network layout presented in Figure 1. To provide a conservative estimate of sensitivity to ClO_4^- across
283 KEs and species, we determined the lowest reported dose observed to activate each KE for each species,
284 regardless of experimental duration. While it is possible that this approach could bias results in AOPs
285 where the timing of activation differs greatly among early and late KEs, no patterns were observed
286 between experimental duration and KE activation in the NIS inhibition AOP, suggesting that ClO_4^-

287 concentration at activation of a KE is an appropriate conservative indicator of sensitivity. We examined
288 the variability both within and among each species and KE by calculating the coefficient of variation
289 (standard deviation divided by mean) for each comparison (Table 2). Results were assembled and
290 plotted in a heatmap comparing species and KEs to summarize species effects and highlight data gaps.

291 3. Results and Discussion:

292 3.1 ClO_4^- case study

293 The data assembled for the ClO_4^- case study focused on toxicity and included empirical dose-
294 response results for 29 endpoints linked to 9 KEs across the AOP network (Table 1). Data points
295 indicating KE activation spanned 7 orders of magnitude (Figure 2) and ranged from 5.0 µg/kg/d for
296 impaired growth in African clawed frogs (Goleman et al. 2002) to 4.14 g/kg/d for LC50 in earthworms
297 (Landrum et al. 2006). The mechanistic nature of the AOP network and conserved KEs facilitated data
298 evaluation across endpoints in human and non-human targets and provided an organizing framework
299 for the display of dose-response data across the species-specific mechanisms of action (Figures 2 and 3).

300 The dose-response data showed relatively flat trends in the amount of ClO_4^- necessary to
301 activate KEs across NIS inhibition AOPs for the species examined, particularly in early and intermediate
302 KEs (Figure 3). The coefficient of variation for the ClO_4^- dose required to activate the early and
303 intermediate KEs (Table 2) was less than two for all species and less than or equal to one for four of the
304 species examined (humans, meadow voles, rabbits, and mosquito fish), indicating relatively little within-
305 species variation. Rats consistently displayed among the lowest reported ClO_4^- doses for KE activation of
306 the species examined, and closely mimicked the human responses hypothesized from the Lumen et al.
307 (2013) model predictions. The fact that KEs within a species were activated at similar concentrations in
308 multiple studies suggests that the AOs in the NIS inhibition AOP are sensitive to the activation of the
309 MIE.

310 Some of the variation in dose-response data for KEs can be explained by measurement
311 limitations, sampling regimes, and differences in experimental techniques among studies. The AOP
312 network (Figure 1) facilitates the interpretation of these results both by describing the sequential
313 relationship among KEs and highlighting data gaps. For example, the lowest doses reported to induce
314 TSH increases in zebrafish and African clawed frogs were approximately 100 fold greater at this KE than
315 at other early and intermediate KEs in these species. However, direct measurement of TSH in these
316 organisms during their development is challenging and sampling efforts were only made at higher doses
317 (Opitz et al. 2006, Schmidt et al. 2012), resulting in an apparent increase in the amount of perchlorate
318 necessary to active this KE. It is likely that this KE is activated at lower doses than those reported for
319 each species, and the fact that KEs both upstream and downstream of TSH increase are activated at
320 lower doses in these species supports this claim (Figures 2 and 3). Similarly, measurements of T4
321 decrease in the plasma of quails were observed at doses over 100 times the upper limit of the dose
322 range reported for other species, but effects were observed at lower activation doses for both upstream
323 and downstream KEs. This finding suggests that more work is required to verify the dose-response
324 relationship for ClO_4^- on TH in the serum of these organisms, despite an observed NOAEL (Figure 2). In a
325 separate example, the ClO_4^- dose ($1.0*10^5$ µg/kg/d; Mukhi and Patiño 2007) required to cause altered
326 jaw development in zebrafish larvae is relatively high compared to other KEs and other species at the
327 development KE. The AOP construct highlights that this finding may be an overestimation because few
328 NOELs for this endpoint have been reported (Figure 2). By highlighting considerations such as these, the
329 AOP network facilitates the evaluation of experimental results from disparate studies across multiple
330 taxa. Additionally, the AOP network enables the organization and interpretation of the results in the
331 context of sequential KEs, rather than individual measurement endpoints.

332 The framework provided by the AOP network also facilitated comparison of the dose-response
333 data across species at each KE. Although the activation doses of ClO_4^- for early and intermediate KEs

334 spanned three orders of magnitude across the organisms examined, four of the species (rats, rabbits,
335 African clawed frogs, and zebrafish) showed activation of at least one KE within the same order of
336 magnitude as the human POD (7.0 µg/kg/d; Figure 3). African clawed frogs and rats were the most
337 sensitive non-human organisms at seven of the nine KEs, suggesting that these species may be more
338 vulnerable than others to ClO_4^- exposure; however, this apparent sensitivity is likely biased by data
339 availability and sampling effort (Figure 3). For example, data were not available for meadow voles at
340 doses lower that 500 µg/kg/d for any KEs in the NIS inhibition AOP. Therefore, we were unable to
341 confirm NOELs at concentrations similar to the human POD and the apparent lack of sensitivity (higher
342 ClO_4^- dose needed for KE activation) for meadow voles observed in Figure 4 is likely an underestimation
343 driven by experimental design. Taken in total, similar trends were observed in data reported in studies
344 across species and KEs (Figure 4), a finding that reflects the highly conserved nature of HPT axis biology
345 among vertebrate organisms (Zoeller et al. 2007). Thus, this case study demonstrates how disparate
346 human health and ecological data sources can be integrated to inform a CRA. However, additional
347 efforts directed at filling in data gaps and testing the same concentrations across species would
348 strengthen the findings.

349 KE activation doses for invertebrate organisms were generally higher than those for vertebrates,
350 but were lower than those for fish at the impaired reproduction, developmental effects, and mortality
351 AOs (Figures 2). This finding may be the result of limited testing efforts at lower concentrations in fish,
352 as previously discussed. Alternatively, different biology among the diverse taxa that make up
353 invertebrates may cause some species to be more sensitive to ClO_4^- exposure than others. For example,
354 the two LC50 data points for the mortality AO correspond to earthworms (4.14 g/kg/d; Landrum et al.
355 2006) and mosquito larvae (74 mg/kg/d; Sorensen et al. 2006), and differences between the ADME
356 properties of these organisms may account for this discrepancy (Figure 2). However, the fact that
357 invertebrates showed responses within the same order of magnitude as vertebrates for AOs, despite

358 lacking an HPT axis, gives support to the hypothesis that control pathways similar to the NIS inhibition
359 AOP are present in these organisms. This finding highlights the utility of the approach presented in this
360 work to leverage the conserved mechanism of action for ClO_4^- to integrate and interpret data across
361 species.

362 The joining of the AEP framework to the AOP framework is essential for the application of the
363 data integration techniques described in this case study to CRA. Relevant TSEs derived from site-based
364 AEPs can be used in conjunction with toxicity data describing KEs in the multi-species AOP network for a
365 community risk assessment. The generalized AEP presented here serves to highlight the relevant
366 exposure pathways that might be considered in a place-based CRA for ClO_4^-. Exposures experienced by
367 different organisms can be projected onto the dose-response data for KEs in the AOP network to
368 identify species at risk. For example, the ClO_4^- case study demonstrates that vertebrate organisms
369 exposed to environmental conditions leading to TSEs of 100 µg/kg/d, including humans, mammals, fish,
370 amphibians, and birds, would also be at risk for NIS inhibition and the downstream KEs and AOs in the
371 NIS inhibition AOP network (Figure 3). Using the same logic, the dose-response data assembled in this
372 case study suggest that ClO_4^- exposures leading to the EPA RfD of 0.7 µg/kg/d (EPA 2005; Figure 2) would
373 not result in high risk of AOs in either human health or ecological endpoints from NIS inhibition.

374 3.2 AEP-AOP construct applications in CRA

375 Hazard identification, exposure, and toxicity have long been recognized as integral components
376 of human health and ecological risk assessment (Barnes et al. 1988, NRC 2009, de Lange et al. 2010).
377 The combined AEP-AOP construct provides a framework for integrating data that spans a source-to-
378 outcome continuum across human health and ecological endpoints (Teeguarden et al. 2016) and
379 facilitates place-based, community-scale applications of the phased approach to CRAs described in
380 Menzie et al. (2007). In the Menzie et al. (2007) approach, a conceptual model is first constructed,

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381 environmental hazards are then identified, and the individual and combined effects of hazards are
382 assessed through toxicity screening. The CSM for relevant exposure mechanisms is extracted from the
383 AEP and the conceptual model for toxicity effects is captured in the AOP network. Multiple stressors
384 can be accommodated easily by assembling the CSM from multiple AEP networks covering the stressors
385 of interest. This can also include transformational relationships among the AEPs whereby one stressor is
386 converted into another. The chemical-agnostic nature of AOP networks (Villeneuve et al 2014a, Edwards
387 et al. 2016) implies that any number of stressors affecting an MIE individually or in concert could be
388 evaluated by converting TSEs to equivalent doses informed by toxicity testing. Thus, the AEP-AOP
389 construct enables the combination of exposure from multiple chemicals and stressors with relevant
390 toxicity data, as advocated by World Health Organization's International Programme on Chemical Safety
391 (Meek et al. 2009) and the National Academies of Sciences, Engineering, and Medicine (NASEM 2017),
392 to inform cross-species CRA.

393 While the ClO_4^- case study presented in this work focused on a single substance to provide a
394 simple example of how the AEP-AOP construct can organize and integrate data across species, the NIS
395 inhibition AOP network used in this work is relevant to all chemicals that perturb the NIS inhibition MIE
396 or other KEs in the network. Therefore, exposure and toxicity data for other NIS inhibitors such as
397 nitrate and thiocyanate (Pickford 2010, Yarrington and Pearce 2011, Pearce and Braverman 2017) could
398 be combined with perchlorate data, and cumulative risk could be assessed based on the exposures of
399 each substance described by the AEP network (Meek et al. 2009, NASEM 2017). For chemicals with
400 complex relationships between environmental exposure and TSEs, species specific information on the
401 ADME properties of a contaminant can be incorporated into PBPK models to quantitatively describe the
402 mechanistic links between the AEP and AOP networks (Clewell, R., in prep). The resulting AEP-AOP
403 continuum can qualitatively assess risk across human health and ecological endpoints to identify species
404 of concern, or can be used quantitatively to calculate species-specific hazard indices such as those as in

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405 Price et al. (2012). However, caution should be taken when conducting quantitative analyses to ensure
406 that a consistent set of doses with relevant experimental conditions has been tested across species as
407 well as across KEs in the AOP network to avoid observational bias.

408 The AEP-AOP approach presented in this work employs the AOP framework differently from
409 toxicity screening applications such as those presented in Angrish et al. (2015) and Knapen et al. (2015).
410 Instead of identifying potentially hazardous chemicals, the AOP network highlights similarities and
411 differences among species responses to contaminants, and can be used in support of site-specific
412 community decision making. The mechanistic emphasis of the AEP-AOP approach provides a systematic
413 construct for communities to both understand components of risk characterization and voice valuation
414 preferences, regarding either exposures or species and endpoint of interest, and decision makers are
415 afforded a more comprehensive characterization of alternatives and impacts. Thus, the AEP-AOP
416 approach readily informs decision support tools such as multi-criteria decision analysis (MCDA; Kiker et
417 al. 2005). Additionally, the organization of data provided by the AEP-AOP construct identifies data gaps
418 that can guide future research. Thus, the techniques presented in this work can highlight what studies
419 will be most informative for risk assessment and help to prioritize future efforts.

420 3.3 Towards a mechanistic approach for place-based community CRAs

421 Developing a site-specific CSM based on AEPs for an area of concern should be an early goal for
422 conducting community based CRAs. These AEPs could be either qualitative or quantitative in nature,
423 depending on the substance(s) and availability of data, and describe the drivers of risk for the organisms
424 inhabiting the study site. Recent work has encouraged a paradigm shift for risk assessments that
425 focuses first on exposure, then on toxicity (Pastoor et al. 2014). The AEP-AOP construct facilitates a
426 mechanistic application of this paradigm by linking exposure information in the form of an AEP network
427 to toxicity for individual KEs in an AOP network.

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428 Connecting toxicity data across species with KEs can be challenging and illustrates the need for a
429 common ontology across disciplines. A KE for an AOP can be described in term of specific processes and
430 objects based on existing biological ontologies (Ives et al. Submitted). For example, the impaired growth
431 KE in the ClO_4^- case study could be assigned the "growth" process term from the Gene Ontology
432 (Ashburner et al. 2000). These biological process and objects can be further related to specific
433 ontological terms from ontologies focused on experimental measurements or toxicological outcomes.
434 For example, in the ClO_4^- case study the growth process can be related to endpoints such as "body
435 weight", "height growth measurement", and "growth condition" from the Experimental Factor Ontology
436 (Malone et al. 2010) to allow endpoints to be matched to KEs in searchable databases. This functionality
437 could contribute to automated population of dose-response data into cross-species AOP networks.
438 Furthermore, adherence to reporting criteria for toxicological data such as those presented in Hanson et
439 al. (2017) could assist in the development of these ontologies and help to ensure that high quality data
440 are available for risk assessments. Combining well-described AOPs with an ontology linking KEs to
441 measurement endpoints will increase the utility of the AEP-AOP construct for integrating human health
442 and ecological endpoints into CRA.

443 The techniques presented in this work demonstrate how a joint AEP-AOP construct can be used
444 to integrate data on human health and ecological endpoints. This approach can advance CRA
445 applications in at least four ways. First, the AEP-AOP construct facilitates the organization of data into
446 mechanistic pathways linking sources of contamination to outcomes in multiple species (Figure 1). This
447 organization provides a common basis for comparing the results of exposure and toxicity experiments
448 and can be used to link a CSM for place-based community CRA to toxicity data. Second, the AEP-AOP
449 construct can inform the evaluation of risk across communities by integrating data from studies
450 spanning multiple taxa (Figure 2). This approach can provide insight into vulnerable populations,
451 elucidate differences and similarities in sensitivity among species, and inform decision support tools

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such as MCDA. Third, the AEP-AOP construct highlights data gaps and can identify areas where more data would be most useful (Figure 4). Identifying and understanding the effects of data gaps is an essential task for guiding the interpretation of existing data and identifying research needs. Furthermore, organizing the information in a systematic way highlights the caveats associated with those data (Figure 2-4). Finally, the AEP-AOP construct emphasizes the need for a common ontology to guide the integration of endpoints across species. The mechanistic approach for cross-species data integration described in this work represents an important step for informing CRA.

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662 **Table 1**: The measurement endpoints for dose-response data that are aggregated into nine key events
663 of the AOP network. Species with data included in this study for at least one of the endpoints at each
664 KE are shown in the Empirical Data column.

Position	KE	Endpoints	Empirical Data
MIE	NIS inhibition	NIS inhibition	Human Rat
Intermediate KEs	TH depletion in thyroid	T4 decrease (thyroid tissue) Colloid depletion	Rat Vole Quail Rabbit Zebrafish Mosquito fish African clawed frog
	TH decrease in serum	T4 decrease (plasma) T3 decrease (plasma) T4 decrease (whole body)	Rat Vole Quail Rabbit Zebrafish Mosquito fish African clawed frog
	TSH increase	TSH increase (whole body) TSH gene upregulation	Rat Zebrafish African clawed frog
	Other thyroid histology changes	Angiogenesis Follicle cell height decrease Hyperplasia Hypertrophy Total thyroid weight	Rat Vole Quail Rabbit Zebrafish Mosquito fish African clawed frog
AOs	Impaired growth	Total body weight Length Condition factor Limb size Altered metamorphosis Altered feeding	Zebrafish African clawed frog Mosquito larvae Sand Dollars Water fleas
	Decreased fecundity	Decreased egg volume Altered sex ratio Altered pubertal development Decreased cocoon production Decreased reproductive output	Zebrafish African clawed frog Earthworms Water fleas
	Developmental neurotoxicity	Altered behavior Altered larval development Altered brain morphometry	Rat Zebrafish African clawed frog
	Decreased survival	LC50 Decreased survival	Mosquito fish Earthworms Mosquito larvae

Table 2:

Coefficients of variation (CV) for the lowest reported activation dose across early and intermediate (E/I) KEs and all KEs the species examined in this study. NA indicates not applicable; * indicates based on modeled results.

Organism	CV (E/I KEs)	CV (all KEs)
Humans (*Homo sapiens*)	0.9*	NA
rats (*Rattus* sp.)	1.3	1.4
meadow voles (*Microtus* sp.)	0.17	0.17
rabbits (*Oryctolagus cuniculus*)	1.0	1.0
African clawed frog (*Xenopus laevis*)	1.1	1.6
zebrafish (*Danio rerio*)	1.9	2.2
mosquito fish (*Gambusia holbrooki*)	0.44	2.0
bobwhite quail (*Colinus virginianus*)	1.7	1.7

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Figures:

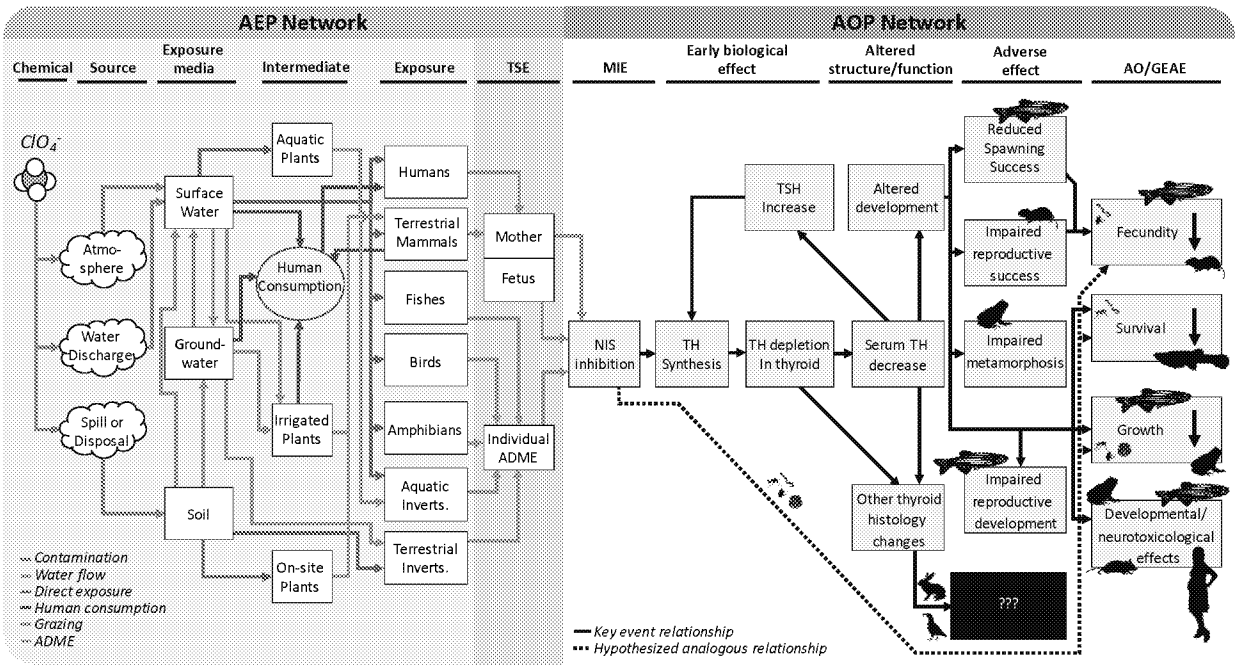

Figure 1: The joint AEP-AOP construct applied to the ClO_4^- case study. White clouds represent different exposure media, while white boxes rectangles represent KESs in the AEP and the purple circle represents the sum of human consumption from KESs. Different colored pathways in the AEP depict different KTRs. Yellow boxes and black arrows depict KEs and KE relationships in the AOP, and the black box represents the unknown effects of thyroid histology changes. Silhouettes of different species show how species-specific AOPs were integrated into the AOP network.

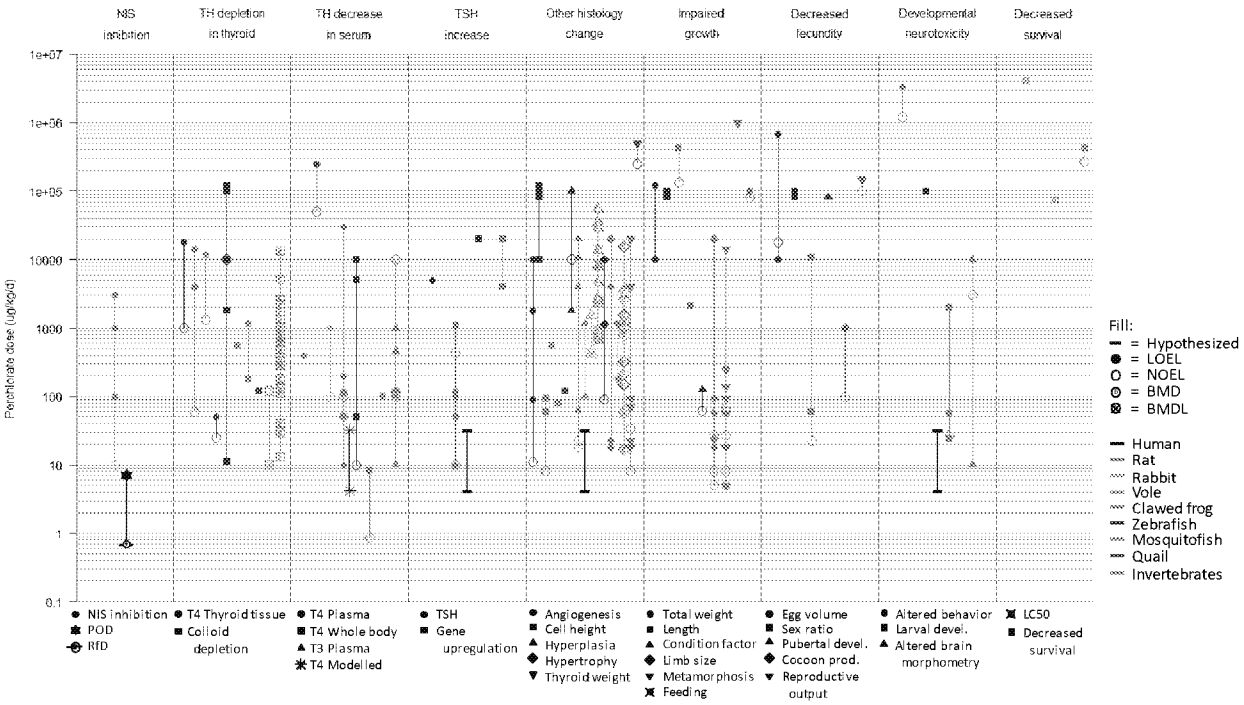

Figure 2: Dose-response data for the nine aggregated KEs in the ClO_4^- AOP network. Each data point represents a different study result, and the point fill represents the type of data. The shape of points corresponds to the legend beneath each KE column, which specifies the measurement endpoint. Colors depict different species, and vertical lines link studies with the same endpoints in the same species. Black asterisks and vertical line in the "TH decrease in serum" KE show the range of predictions from the Lumen et al. (2013) model for hypothyroxinemia based on daily iodide intakes of 200 µg (top) and 75 µg (bottom) to represent iodide sufficient and deficient populations, respectively. Black lines in KEs downstream of "TH decrease in serum" show the hypothesized activation of KEs in humans based on upstream events.

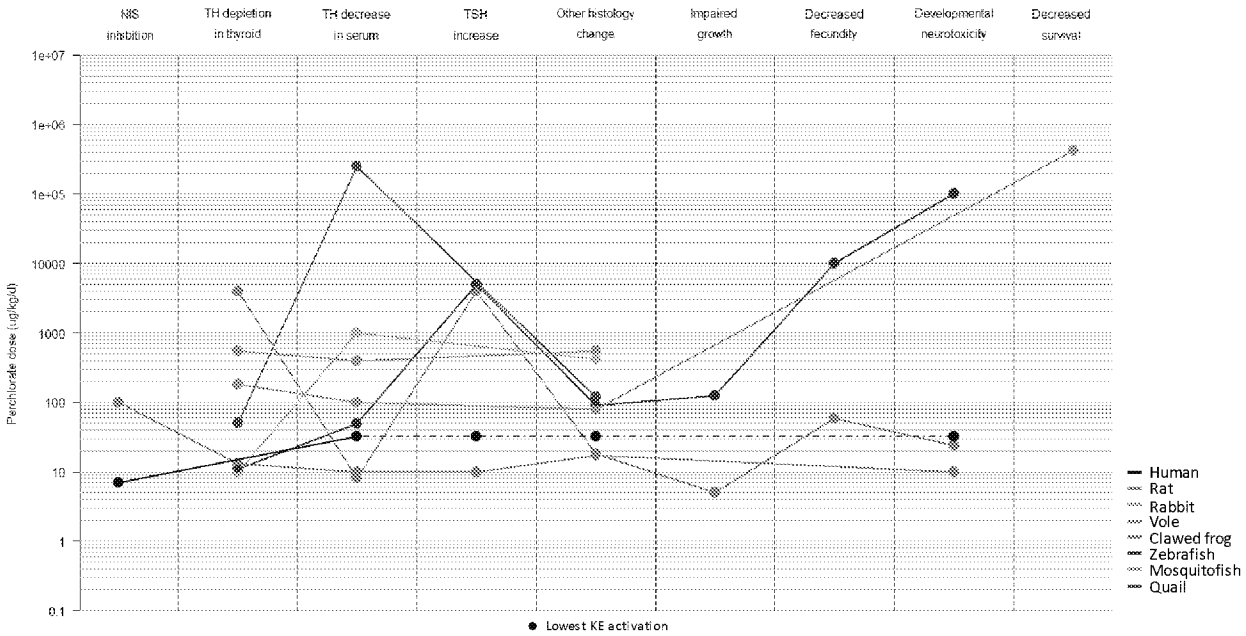

Figure 3: Trajectories of the lowest endpoint observed to activate each KE in the ClO_4^- AOP network for vertebrate each species. Dotted black line for human indicates that the points shown for these KEs are hypothesized from the Lumen et al. (2013) model results for pregnant women receiving 200 µg iodide per day.

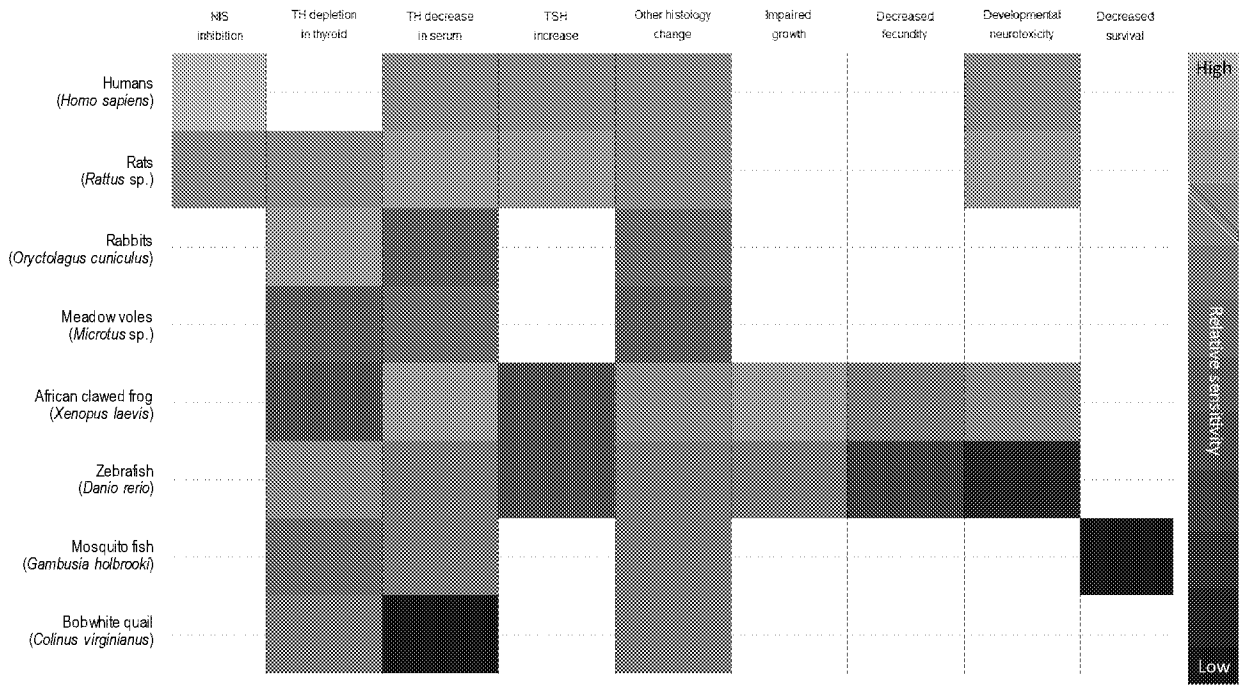

Figure 4: Heatmap showing the relative sensitivity of different vertebrate species to each KE in the ClO_4^- AOP network. Colors correspond to the lowest reported values to activate each KE, with orange indicating lower doses of ClO_4^- necessary for activation. Blank spaces indicate data gaps for each species.

August, 2017

NHEERL Fact Sheet

The Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks facilitate the integration of human health and ecological endpoints for Cumulative Risk Assessment (CRA)

To be submitted to *Environmental Science & Technology*

David E. Hines[1], Stephen W. Edwards[1], Rory B. Conolly[1], and Annie M. Jarabek[2]

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Impact Statement:
This paper contributes to efforts in the Human Health Risk Assessment (HHRA) research program to develop approaches that support cross-species data integration into cumulative risk assessment (CRA) (HHRA Task 6.1). More specifically, this work applies modeling techniques to integrate human health and ecological indicators (Subtask 6.1.3). We discuss how the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks can be used to organize and evaluate exposure and dose response data across multiple species and endpoints. When combined, these frameworks have the potential to provide an organized construct for considering the available data and informing considerations of the mechanistic determinants of risk across species and exposure scenarios. Furthermore, this construct can guide the assembly of existing information that might be used to infer possible exposure scenarios or toxicities in cases where direct data are limited or don't exist. We present a case study focused on an AOP affected by the perchlorate anion (ClO_4^-) in multiple taxa to demonstrate the potential application of this mechanistic approach for cross-species data integration. We highlight that, when coupled with a similar organization of exposure information using the AEP framework, this technique could provide a mechanism-based approach to CRA, and thereby could inform HHRA risk assessments.

Background:
AOPs describe mechanistic linkages between molecular initiating events (MIEs), which result from exposure to a contaminant or stressor, and adverse outcomes (AOs) in an organism. These mechanistic linkages are explicitly represented as a causal series of key events (KEs) and key event relationships (KERs) that span multiple levels of biological organization. We chose to conduct a case study on ClO_4^- because this contaminant activates the sodium-iodide symporter (NIS) inhibition AOP, a well-documented pathway affecting biological mechanisms that are conserved across vertebrate species. The NIS inhibition AOPs for individual species shared several KEs and KERs, allowing the assembly of a cross-species NIS inhibition AOP network that describes the mechanisms leading from a single MIE (NIS inhibition) to multiple AOs from different species. We used this AOP network as a framework to integrate toxicity data from both human health and ecological endpoints and discuss the application of this approach to advance CRA.

Study Description:
We assembled a NIS-inhibition network for eight representative vertebrate species that spanned multiple taxa. Mammals were represented by humans, rats (*Rattus* sp.), meadow voles (*Microtus*

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sp.), and rabbits (*Oryctolagus cuniculus*), while amphibians were represented by the African clawed frog (*Xenopus laevis*), fishes were represented by zebrafish (*Danio rerio*) and mosquito fish (*Gambusia holbrooki*), and birds were represented by the bobwhite quail (*Colinus virginianus*). Data for four invertebrate species, earthworms (*Eisenia foetida*), mosquito larvae (*Culex quinquefasciatus*), the water flea (*Daphnia magna*), and the sand dollar (*Peronella japonica*), were also considered in this study. Model outputs and dose-response data for a total of 29 endpoints from 9 KEs in the AOP network were assembled from the literature and used to demonstrate cross-species integration.

Results:
The AOP framework facilitated evaluation of dose-response data both across KEs and across species. Dose information across all species was converted to a μg/kg/day equivalent to match the data used for human modeling. We observed similar patterns in the dose-response data for the amount of ClO_4^- necessary to activate KEs across the AOP for non-human mammals and amphibians. These trajectories across the AOP were consistent with predictions for activation of KEs in humans based on a published model. The dose-response data assembled for fish and birds contained more variability across KEs than mammal data and showed a departure from the human model predictions. However, the AOP framework revealed data gaps for fish and birds, especially at lower doses, suggesting that additional work is needed to confirm this finding and highlighting the utility of this approach for data interpretation. We also observed a general concordance across species with regard to dose of ClO_4^- necessary to activate the MIE and early KEs, suggesting similar susceptibility to ClO_4^- exposure across the taxa examined. This finding suggests that the current risk assessment based on human health should be protective and could be utilized to characterize risk to other species as well. Our results also suggest that measurements of early KEs should be sufficient to predict adverse outcomes, thereby reducing the cost and increasing the throughput of further testing if needed.

Conclusion:
The techniques discussed in this work 1) provide a mechanistic framework for organizing data from studies with different endpoints across diverse taxa, 2) highlight crucial knowledge gaps, and 3) facilitate the evaluation and integration of toxicological effects for both human health and ecological endpoints. The chemical-agnostic nature of AOPs implies that these tools can be used to examine multiple substances affecting the same MIE, thus AOPs are well suited to inform CRA. Furthermore, AOP networks can be linked to AEP exposure models to provide a source-to-outcome continuum for site-specific, community-scale CRA. While the focus of this work was on the methods and approach to integrate data across species, our findings also support the current human health-based reference dose as protective for both humans and ecological species and thus could be used to characterize ecological impacts.

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Encouraging the Physiologically-Based Pharmacokinetic (PBPK) Modeling Community to Meet the Rigors of Regulatory Review

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Running Title: Facilitating Regulatory Acceptance of PBPK Models

Abstract

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The development and application of physiologically based pharmacokinetic (PBPK) models in chemical toxicology has grown steadily since their emergence in the 1980s. However, the critical evaluation of PBPK models to support regulation across federal agencies has thus far occurred for only few environmental chemicals. In order to encourage decision makers to embrace the critical role of PBPK modeling in regulatory toxicology, several important challenges require immediate attention from the modeling community. The objective of this contemporary review is to highlight some of these challenges, including: (1) difficulties in identifying peer reviewers with appropriate PBPK modeling experience; (2) lack of confidence in PBPK models for which no data exist for model evaluation; and (3) lack of consensus on computing platforms. Several ideas for approaches to address these three issues are provided to initiate dialogue among members of the PBPK modeling community, as these issues must be overcome in order for the PBPK modeling field to advance.

Keywords: physiologically based pharmacokinetic model, good modeling practice, risk assessment, intra-species extrapolation, inter-species extrapolation

A HISTORY OF PBPK MODELING APPROACHES

Physiologically based pharmacokinetic (PBPK) modeling is a valuable tool that arose from the recognition that concentrations of chemicals at target tissues are more predictive of biological responses than are external doses. The number of published PBPK models has risen

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significantly over the past three decades. A search conducted in July 2017 using the PubMed database, with search terms "PBPK OR physiologically based AND pharmacokinetic OR toxicokinetic", reveals that the first published PBPK models were primarily developed for pharmaceutical compounds in the 1970s, followed by those for environmental chemicals in the mid-1980s (Fig. 1). While the number of published models for environmental chemicals quickly outnumbered those for drugs, the latter has recently seen a sharp increase (Fig. 1). Of the 1,313 references describing PBPK models from 1977 to 2016, the majority involve environmental chemicals (65%), followed by drugs (31%), with the remaining 4% involving endogenous compounds like monoclonal antibodies and small peptides.

CURRENT STATUS OF PBPK MODELING IN REGULATORY TOXICOLOGY

Analysis of the extent to which PBPK modeling is currently incorporated into regulatory toxicology and federal level decision-making can shed light on what is needed to increase acceptance of PBPK models in these arenas. The Federal Register (FR) frequently publishes rules, proposed rules, and notices from federal agencies in the United States (US) in an effort to inform the public of changes to government policies and guidelines. The listings found in the FR can serve as a useful barometer for evaluating recent regulatory actions or modeling activities involving PBPK models across the federal government.

A search of the FR in July 2017 using "PBPK" as a keyword returned over 300 related documents spanning from 1988 to 2017 (Table 1). Nearly a quarter of these documents were published either by the US Food and Drug Administration (FDA) or by the US Environmental Protection Agency (EPA), with slightly less than 30% referring to rulemaking processes. The Occupational Safety and Health Administration (OSHA) published 20% of identified FR

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documents, and nearly all involved rulemaking (>90%). The number of PBPK-related FR entries for other agencies covered 26% of identified FRs, with several entries referring to the PBPK modeling efforts in other agencies (e.g., EPA) in support of their rule-making decisions.

Although ~300 FR entries referenced PBPK models, many of them concluded that the limitations and uncertainties inherent in model development precluded their use in risk assessment. For example, a FR issued by the EPA concluded that a published PBPK model for perchlorate cannot be used when establishing a maximum allowable contaminant concentration in drinking water due to inconsistencies in model code, lack of inclusion of a sensitive population, discrepancies between a reference dose provided by the National Research Council and that determined by the PBPK model, and uncertainties in extrapolating animal doses to human-relevant outcomes (FR, 2009). Similarly, OSHA decided that human health risks posed by environmental tobacco smoke were better assessed using abundant epidemiological data compared to a PBPK model for nicotine (OSHA, 1994).

There are some instances in which PBPK models have been used in federal risk assessments and rule making, e.g., OSHA used a PBPK model to describe the pharmacokinetics of methylene chloride (OSHA, 1993). It is challenging to determine the exact number of PBPK models accepted for use by federal agencies based on the FR search alone because the decision to use models is rarely explicitly stated in these documents. Based on our review of these FR entries, we estimate less than 5 - 10% of the mentioned models were eventually applied in regulatory risk assessment.

EPA is one of the two agencies that issued the most PBPK-related FR entries (Table 1), with 26 of the 82 entries being either proposed or final rules for nearly 40 environmental chemicals. Since 2014, several EPA-submitted FR notices have requested experts in PBPK

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modeling. The Office of Water (OW) requested comments on potential reviewers with extensive PBPK modeling experience for evaluation of perfluorooctanoic acid and perfluorooctane sulfonate (FR, 2014). The OW also requested PBPK modeling experts for review of a biologically based dose response model (BBDR) for perchlorate (FR, 2016a). The Integrated Risk Information System (IRIS) program requested peer reviewers with expert knowledge of PBPK modeling to act as members of the Science Advisory Board (SAB) committee for assessing health risks from exposure to hexahydro-1,3,5-trinitro-1,3,5-triazine (FR, 2016b), as well as to tert-Butyl Alcohol, and Ethyl Tertiary Butyl Ether (FR, 2016c). The Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) requested a review of interpretation of chlorpyrifos biomonitoring data using a PBPK-pharmacodynamic (PD) model (FR, 2016d). In 2017, under the Toxic Substances Control Act, the EPA proposed a rule for regulating vapor degreasing that involved acute risk assessment based on PBPK-derived hazard values (FR, 2017). Comprehension and implementation of this rule required input from experts who are familiar with PBPK modeling. These examples suggest that interest in applying PBPK models to support risk assessment of environmental chemicals is increasing.

In addition to involving experts in PBPK modeling in chemical review, the EPA also applies PBPK modeling to support risk assessment and derive toxicity values. A query conducted in July 2017 within the EPA's IRIS program[1] using the keywords "PBPK" OR "PBTK" (TK stands for toxicokinetic) revealed that 50 out of the 511 (~10%) available records reference

PBPK models. Nine of the 50 records involved the use of PBPK models to derive reference dose (RfD) and/or reference concentration (RfC) values (e.g., trichloroethylene, methanol, vinyl

[1] https://www.epa.gov/iris

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chloride), mainly through converting animal points of departure to equivalent human exposure levels, or extrapolating from one exposure route to another. Twenty records suggested that PBPK models may be used in the future when they become available. Three records used PBPK models to support risk assessment in general, such as comparing model predictions with a calculated noobserved-adverse-effect-level (NOAEL) in the case of xylene[2]. Finally, 18 records concluded that existing PBPK models were inappropriate for use by the agency. Reasons behind these conclusions varied, but primarily involved (1) inadequate model structure or parameterization for proper route-to-route or interspecies extrapolation; (2) inadequate description of the pharmacokinetics (PK) of active metabolites; and (3) unavailable human time-concentration data necessary for model validation.

PBPK models are also being applied at the federal level in a non-regulatory capacity. The Agency for Toxic Substances and Disease Registry (ATSDR's) Computational Toxicology and Methods Development Lab has developed models to evaluate exposures to volatile organic chemicals, metals, and persistent contaminants (Ruiz *et al.*, 2010; Ruiz *et al.*, 2011; Mumtaz *et al.*, 2012a). The use of PBPK modeling at ATSDR can be illustrated as follows. In response to community concerns about benzene exposures in Corpus Christi, Texas, ATSDR re-coded a PBPK model developed by Yokley et al. (2006) in Berkeley Madonna (Ruiz et al. 2011; Mumtaz et al. 2012a, 2012b) to predict internal dose metrics from the following three scenarios: (1) occupational exposure leading to minimal adverse non-cancer health effects (0.02 ppm), (2)

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[2] [HYPERLINK "https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0020tr.pdf" \h][HYPERLINK "https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0020tr.pdf" \h][HYPERLINK "https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0270tr.pdf" \h][HYPERLINK "https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0270tr.pdf" \h]https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1011tr.pdf

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continuous exposure to benzene at the ATSDR chronic minimal risk level (MRL; 0.009 ppm), and (3) ambient air exposure levels reported at a stationary air monitor in Corpus Christi (0.1 ppb). The dose metric selected for the internal dose comparison was the cumulative amount of benzene metabolized. While model results were not meant to be predictive of harmful health effects, they suggested that the internal dose of benzene metabolized from Refinery Row residential exposure is 400-fold lower than benzene metabolized at the chronic inhalation MRL level of exposure, and 800-fold lower than benzene metabolized at the occupational level of exposure. (ATSDR, 2016).

The large gap between the numbers of PBPK-related publications (~1,300 from searches in PubMed) and FR notices or IRIS registries (~350) may be due to several factors. First, PBPK models developed for specific academic purposes are often not directly usable by regulatory agencies because model scope, assumptions, and inputs/outputs are not tailored to regulatory needs. Second, the peer review process of a journal seldom requires detailed review of mathematical equations or model code. In contrast, PBPK models that are used to support regulatory toxicology require thorough vetting of model structure, biological characterization, parameter values, computational implementation, and predictive capabilities (McLanahan *et al.*, 2012; US EPA, 2006; WHO, 2010). In this contemporary review, three key issues that stem from the rigorous review required by regulatory and non-regulatory agencies are identified and discussed in the following sections.

KEY ISSUE 1: CHALLENGES IN MODEL REVIEW

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Application of PBPK models offers great potential for informing critical decisions related to public health concerns, but there are significant barriers to the adoption and use of these models to support decision-making. These barriers include:

1. A shortage of individuals with sufficient training to shepherd a modeling project from problem formulation and biological characterization, through model development and coding, to applications in risk assessment (Barton et al., 2007).
2. A shortage of independent reviewers with sufficient expertise in PBPK modeling and regulatory risk assessment to adequately evaluate the validity of conclusions based on PBPK modeling in a timely fashion.
3. A lack of consistent or standardized vetting or submission processes existing across different agencies, by which PBPK models could gain increased acceptance.

Very few academic programs offer comprehensive training in PBPK modeling and application, but some limited alternative training opportunities do exist. Intensive weeklong training programs have been offered for over a decade at Colorado State University and at ScitoVation (previously the Hamner Institutes). These programs, which are appropriate for beginner modelers, risk assessors, and toxicologists have trained many individuals and continue to fill the gap in PBPK modeling education. Additionally, a new online course in PBPK modeling, offered through Kansas State University's Global Campus, provides a unique opportunity for both traditional and non-traditional students to access formal training in computational toxicology. Programs offered at the University of Buffalo and Virginia Commonwealth University, and courses hosted by software companies (e.g., GastroPlus,

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Simcyp, MATLAB) provide additional training opportunities. Collectively, these programs ensure that training in PBPK modeling continues to be available, and that best modeling practices in the field are taught sufficiently.

In addition to training, harmonized templates for model submission and review could encourage the refinement and broad embracement of best practices in PBPK model development and applications. These templates could also provide a standardized process for model review, thus reducing burden on reviewers, and in turn, increasing the likelihood of model adoption at federal and state public health agencies. Some suggested considerations to be included in these templates are presented in further detail below.

Generally, the development of PBPK models for application in risk assessment proceeds in the following four steps (WHO, 2010; Rietjens *et al.*, 2011):

1. Problem formulation
2. Development of model structure, including parameter estimation and mathematical and computational execution
3. Pharmacokinetic simulation and model refinement
4. Model validation and evaluation

In order to increase transparency and ensure that independent reproduction of simulations is possible, model code that is not directly submitted to public health agencies must be provided in conjunction with published manuscripts. While some PBPK modelers publish model code in the supplementary materials, this is a relatively rare practice. Even in instances when model code is made available, annotation is often insufficient to fully recreate the analyses. Increased attention to model quality and documentation would significantly enhance the ability of students,

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reviewers, and users to understand how the model was developed, refined, and applied to reach specific conclusions. Furthermore, careful documentation and quality control will also render the model more apt to be repurposed for other applications and by other users, such as regulatory agencies.

For models that are specifically developed and submitted to support regulatory risk assessment, it is imperative that modelers provide a brief summary of basic model characteristics, including the species, chemical, age/life stage, exposure scenarios, and target organ(s). The modelers should clearly identify the scope of the model, the domain for which the model has been calibrated, and the type of assessment supported by the model (e.g., route extrapolation or species extrapolation), in order to allow for reviewers to evaluate the appropriateness of model structure, parameterization, and applications. A graphic conceptual schematic of the model design is also helpful for visually depicting each model compartment, routes of administration/exposure and excretion, and chemical transport and transformation that occur within the biological organism. Additionally, annotation within the code and related datasets (e.g., values and sources of model parameters) should indicate how different parameter sets correspond to their respective simulated scenarios (e.g., routes, species). Ultimately, this documentation should provide reviewers and risk assessors with sufficient information to understand the model assumptions, independently reproduce simulations, and evaluate the quality of the analysis and validity of the resulting conclusions.

KEY ISSUE 2: LACK OF CONFIDENCE IN MODEL EXTRAPOLATION

PBPK modeling has been recognized as a scientifically sound tool for eliminating or

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replacing the default extrapolation factors, such as a 10X for interspecies (animal to human) and a 10X for intra-species (average to sensitive population), that are commonly applied in regulatory risk assessment (EPA, 2006; Martin *et al.*, 2013; Poet *et al.*, 2016; Thompson *et al.*, 2008; Valcke and Krishnan, 2014). When little or no human *in vivo* data is available to evaluate the concordance between model predictions and observed data, risk assessors are faced with the challenge of defending their use of human PBPK models developed with chemical-specific parameters based on *in vivo* and *in vitro* animal data, and sometimes, *in vitro* human data (Bois *et al.*, 2016; DeWoskin *et al.*, 2013; El-Masri *et al.*, 2016).

This challenge can be illustrated using a recent example in which the FDA conducted computational research to evaluate Bisphenol A (BPA) toxicity[3]. For BPA, several PBPK models based on various pharmacokinetic studies carried out with rats and nonhuman primates were available in the literature (Fisher *et al.*, 2011; Yang *et al.*, 2013; Yang *et al.*, 2015; Yang and Fisher, 2015). The animal models were then scaled to humans to predict time profiles for unconjugated BPA (the biologically active form), without the benefit of human data available at the time. Sometime later, two human PK studies were conducted, and when previously developed PBPK models (Edginton and Ritter, 2009; Mielke and Gundert-Remy, 2009; Teeguarden *et al.* 2005, Fisher *et al.*, 2011) were not able to properly predict serum concentrations of BPA for humans, these models required recalibration using the human data from the PK studies (Fig. 9 in Yang *et al.* 2015).

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[3] [HYPERLINK "https://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM424266.pdf" \h][HYPERLINK "https://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM424266.pdf" \h]

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To further investigate the common nature of this challenge, published human models were extracted from a PBPK knowledgebase (KB) (Lu *et al.* 2016). The PBPK KB includes 795 articles, published between 1977 and 2013, that have PBPK models for approximately 300 chemicals. Using the query term: ["human" AND "rat" OR "mouse" OR "dog" OR "monkey" OR "rabbit" OR "guinea pig" OR "sheep" OR "pig" OR "cow" OR "hamster" OR "horse"] returned 145 peer-reviewed articles. Five articles were picked due to the keyword "human" found in the abstract, to reference future development of a human model, but these articles were excluded because they did not contain human models. Additionally, ten publications were excluded since they only referenced previously published human models.

The remaining 130 publications that contained both animal and human models were further divided into the following three groups: (1) those providing predictions from human PBPK models, but having no human *in vivo* time-concentration or time-response data available for comparing to model predictions (N = 40); (2) those in which human *in vivo* time-concentration or time-response data are used to calibrate human PBPK models (N = 46); and (3) those in which model predictions and available human *in vivo* time-concentration or time-response data agreed, thus requiring no additional calibration using human *in vivo* data (N = 44).

The studies in group 1 are primarily academic exercises that applied human PBPK models to understand the PK behavior of a chemical and its impact on the relationship between external and internal exposure. However, when the purpose is to support regulatory decision-making, little confidence is given to human PBPK models that cannot show concordance between model predictions and observed data. In cases where human timeconcentration or time-response *in vivo* data are available (groups 2 and 3), we found similar numbers of publications that used human data for optimizing human parameters to

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align predictions more closely with observations (group 2) and that simply used human data to demonstrate a model's predictive capability without further adjustment to model parameters (group 3). Our analysis suggested that allometric scaling is appropriate at times (group 3), and the primary difference between these two groups is that the model structure of the former is more empirical than the latter.

Parameters in a PBPK model are obtained from literature (e.g., blood flow to tissues, tissue volumes), measurements (e.g., partition coefficient between air and blood), or optimized by fitting model predictions to data (e.g., oral absorption rate). Most published studies in group 2 have taken the 'top-down' modeling approach, in which various biochemical processes are lumped to present the simplest model structure that is capable of reproducing available time-concentration *in vivo* data. For example, adjusting one clearance rate may be sufficient to fit model predictions to rat plasma concentration data. Such an approach is common when the purpose of a study is to organize mechanistic data and present the state of knowledge regarding the PK behaviors of a chemical. The simplicity of the model structure may negate the need to conduct additional studies to characterize PK processes, but it often requires recalibration of a human model based on human data, as differences in some physiological or biochemical processes between species cannot be captured by a single parameter (e.g., metabolism rate or oral absorption rate).

In contrast, many published studies in group 3 developed human PBPK models using a 'bottom-up' approach. The model structure for such an approach is based more on a mechanistic understanding of PK processes, and values of model parameters are often derived from *in vitro* or *in silico* methods, as opposed to calibrated using *in vivo* data. Mechanisticbased model parameters, such as tissue-specific expression of enzymes or multicompartmental absorption rates, allow for incorporating species-dependent, gender-

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dependent, and life stage-dependent variability into the model, and thus, their impact might be assessed

on target tissue doses or other model outputs. Also, simple allometric scaling from animals to humans is shown in several studies in group 3 to be adequate to construct a human version of the PBPK model without further adjustment of parameters, especially for volatile organic compounds.

Over time, the risk assessment paradigm has shifted away from use of traditional whole animal toxicity testing due to advancements in molecular biology, toxicology, and computing. As a result, the scientific community has developed methods that are more efficient and effective, and less expensive, for assessing human health risks posed by exposure to environmental chemicals (Krewski *et al.*, 2010). In light of this shifting paradigm, the PBPK modeling community is also reassessing traditional modeling approaches that are based on *in vivo* animal data, and starting to embrace novel *in vitro* and *in silico* technologies capable of more efficiently generating PBPK models that can be more mechanistic-based and predictive. By no means does this require a complete reinventing of modeling approaches, as *in vivo* data are still essential for evaluating the predictive capability of a PBPK model that is used to support decisions that require balance between risk and benefits (e.g., for a pesticide, potential neurodevelopment effects vs. elimination of disease-causing insects). The sophistication of PBPK models will continue to increase with incorporation of, and integration with, emerging data such as omics, protein transporters, and pharmacodynamic (PD) or biologically-based dose response (BBDR) models (Abaci and Shuler, 2015; Hamon *et al.*, 2014; Kuepfer *et al.*, 2016). These advancements, at the same time, create additional challenges for the regulatory community attempting to apply these models to assess health risks.

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KEY ISSUE 3: LACK OF CONSENSUS IN COMPUTING PLATFORMS

The choice of computing platforms for PBPK modelers is primarily based on the preference or familiarity of model developers. The growing number of platform choices for coding PBPK models is an obstacle when regulatory agencies attempt to identify independent peer reviewers to perform detailed code review. Another issue with computing platforms is that models coded in software platforms that are no longer in use may need to be recoded in a different program or may not be accessible. The PBPK modeling community has faced these challenges for years, and there is a demand for coordination and interoperability of different modeling platforms. In recent years, several research groups have developed open-source packages (e.g., HTTK[4], MERLIN-Expo[5], RVis[6], PLETHEM[7]), and each is designed for a specific purpose, such as post-modeling processing (e.g., sensitivity analysis) or generating high throughput *in silico* predictions. Therefore, consensus is needed regarding which platform options are best suited for PBPK modeling projects with specific regulatory applications (Jamei, 2016).

CONCLUSIONS AND FUTURE DIRECTIONS

PBPK modeling will remain a vital research, screening, and regulatory tool within our federal agencies. Searches of both the FR and the EPA IRIS database for the use of PBPK modeling clearly demonstrate a growing interest in the incorporation of computational models at

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[4] https://cran.r-project.org/web/packages/httk/index.html

[5] http://merlin-expo.eu/

[6] http://cefic-lri.org/projects/aimt7-rvis-open-access-pbpk-modelling-platform/ [7] http://www.scitovation.com/plethem.html

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EPA. Computational modeling and simulation is also a large enterprise across the FDA. In a non-regulatory capacity, ATSDR has incorporated PBPK modeling in its evaluation of environmental exposures to chemicals to promote public health. There are demonstrated barriers to the acceptance of PBPK modeling in both regulatory and non-regulatory arenas because of challenges in identifying independent peer reviewers with appropriate experience in applying PBPK modeling in regulatory risk assessment, lack of confidence in PBPK models for which no data exist for model evaluation, and a lack of consensus on computing platforms. Efforts to improve training for both model developers and reviewers, as well as to develop templates to facilitate submission and review of PBPK models at public health agencies, offer hope for addressing the challenges described herein. A model submission template that requests elucidation of model scope and purposes could also encourage data collectors and modelers to engage risk assessors during the early stage of model development to ensure that the final model is designed to meet specific needs of risk assessors. Such engagement should also improve communication by making model results more understandable for risk assessors.

There is ongoing discussion and collaboration amongst the computational modeling community, regarding incorporation of increasingly sophisticated techniques for improved model parameterization and extrapolation that does not rely on *in vivo* data. For example, coupling *in vitro* metabolism data with enzyme ontogeny data can be used to estimate agedependent *in vivo* clearance rates. These new techniques, combined with more frequent and open communication of the model development process, pave the way for incorporating models with varying degrees of sophistication in different risk assessment applications, such as screening chemicals for further testing or estimating data-derived extrapolation factors. With explicit documentation detailing the caveats of these different tiers of models, risk assessors can determine the most appropriate application of these models, without having to wait decades

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for an extensively characterized model suited to one specific risk assessment purpose. Furthermore, closer interactions between modelers and risk assessors will facilitate prioritization of future model development based on the capacity of existing models to address the needs of regulatory and non-regulatory assessment of risks posed by environmental chemicals.

Disclaimer

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Figure Legend

Figure 1. Number of articles referencing physiologically based pharmacokinetic models for drugs or environmental chemicals that have been published over the last several decades. The keyword search included "pbpk OR ("physiologically based" AND (pharmacokinetic OR toxicokinetic", resulting in articles first identified in 1977 in the PubMed literature database.

Table 1. Numbers of agency submissions of Federal Register (FR) documents that are identified using the keyword "PBPK".

Federal Agencies	Number of FR entries

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Food and Drug Administration (FDA)	89
Environmental Protection Agency (EPA)	84
Occupational Safety and Health Administration (OSHA)	64
The Agency for Toxic Substances and Disease Registry (ATSDR)	37
National Highway Traffic Safety Administration (NHTSA)	30
The Centers for Disease Control and Prevention (CDC)	11
Mine Safety and Health Administration (MSHA)	2
Office of Surface Mining Reclamation and Enforcement (OSMRE)	2

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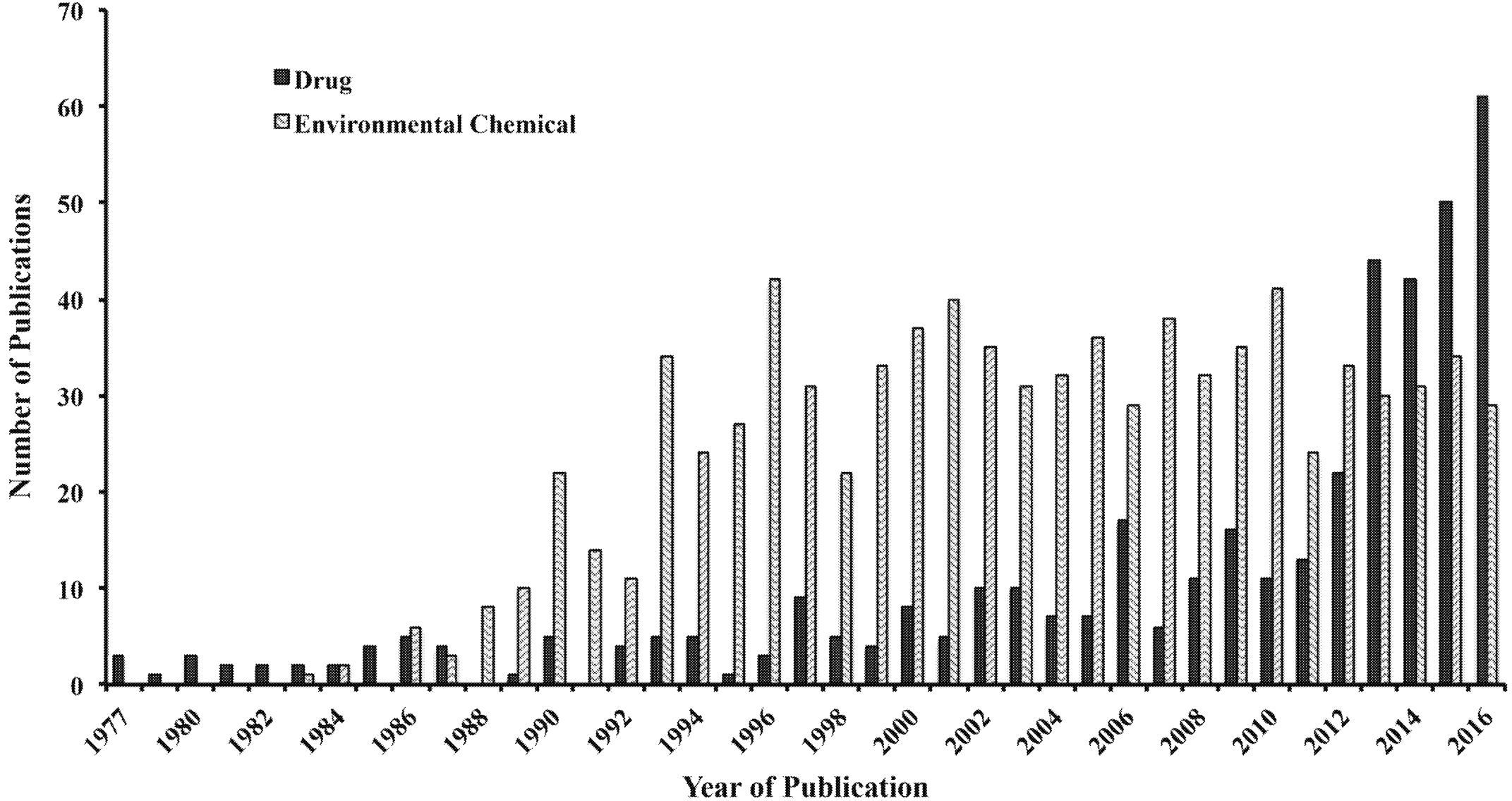
Drug
Environmental Chemical
Number of Publications
0
10
20
30
40
50
60
70
1977
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year of Publication

High-Throughput Screening of ToxCast Phase I Chemical Library for Sodium Iodide Symporter (NIS) Inhibitors

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DISCLAIMER: This manuscript has been reviewed in accordance with the policies of the National Health and Environmental Effects Research Laboratory and National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views or policy of the Agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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Abstract

The U.S. EPA's Endocrine Disruptor Screening Program (EDSP) and Office of Research and Development (ORD) are currently developing high throughput assays to screen chemicals that may alter the thyroid hormone pathway. One potential target in this pathway is the sodium iodide symporter (NIS), a transmembrane glycoprotein that mediates iodide uptake into the thyroid gland as the initial step in thyroid hormone biosynthesis. Our laboratory recently validated a screening approach to identify potential NIS inhibitors using a novel cell line hNIS-HEK293T-EPA. Here, we screened the ToxCast phase 1_v2 chemical library, representing 293 unique environmental chemicals, in the newly developed radioactive iodide uptake (RAIU) assay. First, 310 blinded samples were screened in single-concentration format at 100μM. Using 20% inhibition as the activity threshold, 169 samples reached this criterion and were further tested for concentration-response (0.001 μM - 100 μM) with parallel RAIU and cell viability assays. To facilitate prioritization of potential thyroid toxicants, a unique ranking system that incorporates cytotoxicity responses was developed to sort the RAIU inhibition potency of the chemicals. Chemicals were ranked with a score that is relative to the well-known NIS inhibitor sodium perchlorate. The top ranked 14 chemicals had varying responses in the screening and their diverse toxicological properties are discussed in detail. Further testing is warranted to characterize the nature of the inhibition observed with these chemicals. This study represents the first large-scale screening of environmental chemicals for NIS inhibitors, and supports the U.S. EPA's EDSP21 and OECD in their efforts to develop high throughput screening approaches that expand the coverage of molecular targets of thyroid disruption.

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Keywords: sodium iodide symporter, thyroid, endocrine disruptor, high-throughput *in vitro* screening assay

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Introduction

Thyroid hormones (TH; i.e., thyroxine (T4) and triiodothyronine (T3)) regulate an array of physiological processes that are essential for metabolism, cardiovascular function, bone maintenance, as well as fetal and post-natal neurodevelopment [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Over the past two decades, a number of structurally diverse xenobiotics have been shown to interfere with TH homeostasis and result in physiological and morphological perturbations [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further work in this area has identified multiple molecular targets of chemical-mediated thyroid disruption including the regulation of circulating TH through feedback mechanisms within the hypothalamic-pituitary-thyroid (HPT) axis, TH synthesis and secretion, TH distribution and transport, TH metabolism, and TH receptor binding and action [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These studies demonstrated a need for a better understanding of the structural characteristics of chemicals with thyroid disrupting activity, the potential for environmental exposures, and the possible health risks to humans and wildlife. To address these concerns, the U.S. EPA's Endocrine Disruptor Screening Program (EDSP21, https://www.epa.gov/endocrine-disruption) in concert with the U.S. EPA's Office of Research and Development (ORD) recently expanded the coverage of molecular targets for disruption of the TH pathway by developing and implementing the use of high throughput screening (HTS) assays to identify inhibitors of TH synthesis (e.g., sodium/iodide symporter (NIS) and thyroid peroxidase) and T4 metabolism (e.g., deiodinases). Methods for a thyroid peroxidase assay were previously described by Paul et al. (2014) and used to screen chemicals in the ToxCast phase I_v2 and II chemical libraries [ADDIN EN.CITE

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<EndNote><Cite><Author>Paul Friedman</Author><Year>2016</Year><RecNum>82</RecNum><DisplayText>(Paul Friedman<style face="italic"> et al.</style>, 2016)</DisplayText><record><rec-number>82</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1493395974">82</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Paul Friedman, Katie</author><author>Watt, Eric D.</author><author>Hornung, Michael W.</author><author>Hedge, Joan M.</author><author>Judson, Richard S.</author><author>Crofton, Kevin M.</author><author>Houck, Keith A.</author><author>Simmons, Steven O.</author></authors></contributors><titles><title>Tiered High-Throughput Screening Approach to Identify Thyroperoxidase Inhibitors Within the ToxCast Phase I and II Chemical Libraries</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>160-180</pages><volume>151</volume><number>1</number><dates><year>2016</year></dates><isbn>1096-6080</isbn><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfw034</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfw034</electronic-resource-num></record></Cite></EndNote>]. In addition, our laboratory recently demonstrated the utility of another HTS assay to detect chemicals that disrupt NIS-mediated transport of extracellular iodide across the cellular membrane [ADDIN EN.CITE

<EndNote><Cite><Author>Hallinger</Author><Year>2017</Year><RecNum>64</RecNum><DisplayText>(Hallinger<style face="italic"> et al.</style>, 2017)</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798592">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hallinger, Daniel R.</author><author>Murr, Ashley S.</author><author>Buckalew, Angela R.</author><author>Simmons, Steven O.</author><author>Stoker, Tammy E.</author><author>Laws, Susan C.</author></authors></contributors><titles><title>Development of a screening approach to detect thyroid disrupting chemicals that inhibit the human sodium iodide symporter (NIS)</title><secondary-title>Toxicology in Vitro</secondary-title></titles><periodical><full-title>Toxicology in Vitro</full-title></periodical><pages>66-78</pages><volume>40</volume><keywords><keyword>Thyroid</keyword><keyword>Endocrine disruptors</keyword><keyword>Sodium iodide symporter</keyword><keyword>Chemical screening</keyword></keywords><dates><year>2017</year><pub-dates><date>4//</date></pub-dates></dates><isbn>0887-2333</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0887233316302569</url><url>http://ac.els-cdn.com/S0887233316302569/1-s2.0-S0887233316302569-main.pdf?_tid=286edb04-d8fa-11e6-b2db-00000aacb360&acdnat=1484248141_9bcc422b76262b7c7843748a566dbb7c</url></relate

d-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.tiv.2016.12.006</electronic-resource-num></record></Cite></EndNote>].

NIS is a glycoprotein with 13 transmembrane helices [ADDIN EN.CITE ADDIN EN.CITE.DATA] that actively transports I^- anions into thyroid follicular cells. This activity relies on the inwardly directed Na^+ electrochemical gradient maintained by Na^+/K^+ ATPases with an electrogenic stoichiometry of 2 Na^+ per I^- [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Under normal physiological conditions, NIS can efficiently enrich iodide into the thyroid gland to achieve a 20 to 40 fold I^- concentration gradient [ADDIN EN.CITE <EndNote><Cite><Author>Dohán</Author><Year>2003</Year><RecNum>5</RecNum><DisplayText>(Dohán<style face="italic"> et al.</style>, 2003)</DisplayText><record><rec-number>5</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1493133346">5</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dohán, Orsolya</author><author>De la Vieja, Antonio</author><author>Paroder, Viktoriya</author><author>Riedel, Claudia</author><author>Artani, Mona</author><author>Reed, Mia</author><author>Ginter, Christopher S.</author><author>Carrasco, Nancy</author></authors></contributors><titles><title>The Sodium/Iodide Symporter (NIS): Characterization, Regulation, and Medical Significance</title><secondary-title>Endocrine Reviews</secondary-title></titles><periodical><full-title>Endocrine Reviews</full-title></periodical><pages>48-77</pages><volume>24</volume><number>1</number><dates><year>2003</year></dates><i

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sbn>0163-769X</isbn><urls><related-urls><url>http://dx.doi.org/10.1210/er.2001-0029</url></related-urls></urls><electronic-resource-num>10.1210/er.2001-0029</electronic-resource-num></record></Cite></EndNote>]. Apart from the thyroid gland, NIS is also expressed in other tissues such as mammary gland during lactation, stomach, and salivary gland [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Disruption of NIS-mediated iodide uptake has been correlated with depressed TH synthesis (hypothyroidism) and adverse health outcomes in humans and animals. For example, patients with various gene mutations leading to aberrant NIS protein have hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Pohlenz</Author><Year>1999</Year><RecNum>97</RecNum><DisplayText>(Pohlenz and Refetoff, 1999)</DisplayText><record><rec-number>97</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1494530226">97</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pohlenz, Joachim</author><author>Refetoff, Samuel</author></authors></contributors><titles><title>Mutations in the sodium/iodide symporter (NIS) gene as a cause for iodide transport defects and congenital hypothyroidism</title><secondary-title>Biochimie</secondary-title></titles><periodical><full-title>Biochimie</full-title></periodical><pages>469-476</pages><volume>81</volume><number>5</number><keywords><keyword>congenital hypothyroidism</keyword><keyword>thyroid</keyword><keyword>iodide transport</keyword><keyword>molecular genetics</keyword></keywords><dates><year>1999</year><pub-dates><date>5//</date></pub-dates></dates><isbn>0300-9084</isbn><urls><related-

urls><url>http://www.sciencedirect.com/science/article/pii/S0300908499800972</url></related-urls></urls><electronic-resource-num>https://doi.org/10.1016/S0300-9084(99)80097-2</electronic-resource-num></record></Cite></EndNote>]. In addition, several monovalent anions including perchlorate (ClO_4^-), thiocyanate (SCN^-), and nitrate (NO_3^-) are known to competitively inhibit I^- uptake by NIS and disrupt TH synthesis in humans [ADDIN EN.CITE ADDIN EN.CITE.DATA] and multiple species of vertebrates [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The identification of the environmental chemicals triclosan, triclocarban, BDE-47, bisphenol A (Wu *et al.*, 2016), and several small drug-like organic molecules as NIS-mediated iodide transport inhibitors [ADDIN EN.CITE ADDIN EN.CITE.DATA] indicates effects on NIS that extend beyond simple competitive inhibition by anions.

We recently developed a radioactive iodide uptake (RAIU) assay to measure uptake of iodide in a novel cell line stably expressing human sodium/iodide symporter, hNIS-HEK293T-EPA [ADDIN EN.CITE

<EndNote><Cite><Author>Hallinger</Author><Year>2017</Year><RecNum>64</RecNum><DisplayText>(Hallinger<style face="italic"> et al.</style>, 2017)</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798592">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hallinger, Daniel R.</author><author>Murr, Ashley S.</author><author>Buckalew, Angela R.</author><author>Simmons, Steven O.</author><author>Stoker, Tammy E.</author><author>Laws, Susan

C.</author></authors></contributors><titles><title>Development of a screening approach to detect thyroid disrupting chemicals that inhibit the human sodium iodide symporter (NIS)</title><secondary-title>Toxicology in Vitro</secondary-title></titles><periodical><full-title>Toxicology in Vitro</full-title></periodical><pages>66-78</pages><volume>40</volume><keywords><keyword>Thyroid</keyword><keyword>Endocrine disruptors</keyword><keyword>Sodium iodide symporter</keyword><keyword>Chemical screening</keyword></keywords><dates><year>2017</year><pub-dates><date>4//</date></pub-dates></dates><isbn>0887-2333</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0887233316302569</url><url>http://ac.els-cdn.com/S0887233316302569/1-s2.0-S0887233316302569-main.pdf?_tid=286edb04-d8fa-11e6-b2db-00000aacb360&acdnat=1484248141_9bcc422b76262b7c7843748a566dbb7c</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.tiv.2016.12.006</electronic-resource-num></record></Cite></EndNote>]. This HTS approach was validated and proved to be a robust, highly reproducible approach for rapidly screening large chemical libraries for inhibitors of NIS-mediated iodide uptake. In the current study, we applied the HTS approach to screen the larger ToxCast phase1_v2 chemical library [ADDIN EN.CITE <EndNote><Cite><Author>Richard</Author><Year>2016</Year><RecNum>66</RecNum><DisplayText>(Richard<style face="italic"> et al.</style>, 2016)</DisplayText><record><rec-number>66</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798627">66</key></foreign-

keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Richard, Ann M.</author><author>Judson, Richard S.</author><author>Houck, Keith A.</author><author>Grulke, Christopher M.</author><author>Volarath, Patra</author><author>Thillainadarajah, Inthirany</author><author>Yang, Chihae</author><author>Rathman, James</author><author>Martin, Matthew T.</author><author>Wambaugh, John F.</author><author>Knudsen, Thomas B.</author><author>Kancherla, Jayaram</author><author>Mansouri, Kamel</author><author>Patlewicz, Grace</author><author>Williams, Antony J.</author><author>Little, Stephen B.</author><author>Crofton, Kevin M.</author><author>Thomas, Russell S.</author></authors></contributors><titles><title>ToxCast Chemical Landscape: Paving the Road to 21st Century Toxicology</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>1225-1251</pages><volume>29</volume><number>8</number><dates><year>2016</year><pub-dates><date>2016/08/15</date></pub-dates></dates><publisher>American Chemical Society</publisher><isbn>0893-228X</isbn><urls><related-urls><url>http://dx.doi.org/10.1021/acs.chemrestox.6b00135</url></related-urls></urls><electronic-resource-num>10.1021/acs.chemrestox.6b00135</electronic-resource-num></record></Cite></EndNote>]. This library of 293 unique chemicals covers a broad spectrum of chemicals that are currently under the U.S. EPA's regulatory purview [ADDIN EN.CITE

<EndNote><Cite><Author>Richard</Author><Year>2016</Year><RecNum>66</RecNum><DisplayText>(Richard<style face="italic"> et al.</style>, 2016)</DisplayText><record><rec-number>66</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798627">66</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Richard, Ann M.</author><author>Judson, Richard S.</author><author>Houck, Keith A.</author><author>Grulke, Christopher M.</author><author>Volarath, Patra</author><author>Thillainadarajah, Inthirany</author><author>Yang, Chihae</author><author>Rathman, James</author><author>Martin, Matthew T.</author><author>Wambaugh, John F.</author><author>Knudsen, Thomas B.</author><author>Kancherla, Jayaram</author><author>Mansouri, Kamel</author><author>Patlewicz, Grace</author><author>Williams, Antony J.</author><author>Little, Stephen B.</author><author>Crofton, Kevin M.</author><author>Thomas, Russell S.</author></authors></contributors><titles><title>ToxCast Chemical Landscape: Paving the Road to 21st Century Toxicology</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>1225-1251</pages><volume>29</volume><number>8</number><dates><year>2016</year><pub-dates><date>2016/08/15</date></pub-dates></dates><publisher>American Chemical Society</publisher><isbn>0893-228X</isbn><urls><related-urls><url>http://dx.doi.org/10.1021/acs.chemrestox.6b00135</url></related-

urls></urls><electronic-resource-num>10.1021/acs.chemrestox.6b00135</electronic-resource-num></record></Cite></EndNote>], as well as a subset of chemicals that have been tested extensively in the Agency's EDSP Tier I Screening Battery [ADDIN EN.CITE <EndNote><Cite><Author>U.S.EPA</Author><Year>2015</Year><RecNum>111</RecNum><DisplayText>(U.S.EPA, 2015)</DisplayText><record><rec-number>111</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1499365200">111</key></foreign-keys><ref-type name="Online Database">45</ref-type><contributors><authors><author>U.S.EPA</author></authors></contributors><titles><title>Endocrine Disruptor Screening Program Tier 1 screening determinations or weight of evidence assessments.</title></titles><dates><year>2015</year><pub-dates><date>July 6, 2017</date></pub-dates></dates><pub-location>https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and</pub-location><urls><related-urls><url>https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and</url></related-urls></urls></record></Cite></EndNote>]. This study expands the current knowledge of NIS inhibition potential of environmentally-relevant chemicals and the results may be used for prioritizing chemicals for further testing and informing the development of adverse outcome pathways for thyroid disruption.

Materials and Methods

Cell Line and Growth Conditions

As described by Hallinger et al. (2017), an HEK293T cell line expressing functional human NIS, hNIS-HEK293T-EPA, was utilized for radioactive iodide uptake (RAIU) and cell viability assays. In brief, low passage hNIS-HEK293T-EPA cells (<30 passes) were cultured in Dulbecco's Modified Eagle Medium (DMEM; Gibco,Waltham, MA) supplemented with 10% newborn calf serum (Gibco, Waltham, MA), 10mM HEPES, 100U/mL penicillin and 0.1mg/mL streptomycin (Sigma, St. Louis, MO) at 37°C in a humidified 5% CO_2 atmosphere. Culture flasks were coated with collagen type I (Corning, Corning, NY) in 0.02N acetic acid solution (4µg per cm^2) and washed with sterile deionized H_2O prior to subculture. All 96-well microplates were coated with 0.01% poly-L-lysine (Sigma, St. Louis, MO) and washed with sterile deionized H_2O prior to cell seeding. Cells were grown to 90 – 95% confluence in T75 flasks (Corning, Corning, NY) before trypsinization in 0.05% trypsin/EDTA (Gibco, Waltham, MA) where cells were sub-cultured in T75 flasks or seeded in 96-well plates as described in assay sections below.

Chemicals

Chemical names, CAS numbers, and maximum concentration tested are shown in Tables 1 (Assay controls) and 2 (Test chemicals). All control chemicals were initially solubilized in DMSO (EMD Millipore Corp., Darmstadt, Germany) at 20 mM and included sodium perchlorate ($NaClO_4$; RAIU assay positive control), sodium nitrate ($NaNO_3$; RAIU assay EC_{80} control), sodium thiocyanate

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(NaSCN; RAIU assay EC_{20} control), 2,4-dichlorophenoxyacetic acid (2,4-D; RAIU assay negative control), and 2,3-dichloro-1,4-napthoquinone (DCNQ; cell viability assay positive) (Sigma Aldrich, St. Louis, MO).

Chemicals of the ToxCast phase 1_v2 library were solubilized in DMSO and provided as 310 blinded samples in five 96-well plates (62 samples per plate) (Evotec Inc., South San Francisco, CA). Of the 310 samples, there were 293 unique chemicals - the remaining 17 serving as internal quality control replicates randomly distributed among the five plates. All chemicals were administered to bioassay plates using a BioMek FX Automated Laboratory Workstation (Beckman Coulter, Indianapolis, IN) equipped with a stainless steel high density replicating (HDR) tool (96-pin) to transport 350nL per well for the RAIU, cell viability, and Sandell-Kolthoff (SK) assays as described below.

Radioactive Iodide Uptake (RAIU) Assay

RAIU assays were conducted as previously described (Hallinger *et al.* 2017). In brief, hNIS-HEK293T-EPA cells were seeded with a MultiFlo FX dispenser (BioTek, Winooski, VT) into ScintiPlate-96 microplates (Perkin Elmer, Waltham, MA) at a density of 4.0×10^4 cells per well in 200μL growth media and incubated for 40 hours before experimentation. On the day of the assay, carrier-free ^{125}I (Perkin-Elmer, Waltham, MA; specific activity: 17.4Ci/mg) was diluted with Hanks' balanced salt solution (Sigma, St. Louis, MO) supplemented with 10mM HEPES (uptake buffer; pH 7.4) at 5μCi/mL (288pg ^{125}I/mL uptake buffer; 2.30nM). The assay was initiated by gently washing cells twice with 200μL uptake buffer using a 96-well Tecan HydroSpeed plate

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washer (Tecan, Männedorf, Switzerland). Uptake buffer (59.7μL) was then added back to each well. Chemical samples (350nL at 200X) were added to each well using the HDR tool as previously described to achieve a 1X chemical/0.5% final DMSO concentration with subsequent addition of 10μL of ^{125}I dilution (final [^{125}I]: 329pM; 2.88pg/well) for a final reaction volume of 70μL/well. With this dilution protocol, a 20 mM stock chemical would have a final test concentration of 100 μM. Cells were incubated at room temperature for 2 hours and then washed twice with 200μL ice-cold uptake buffer. All uptake buffer was aspirated from wells, plates were sealed, and read on a MicroBeta^2 plate reader (Perkin Elmer, Waltham, MA) using a detection protocol to measure CPM corresponding to intracellular ^{125}I concentration. Assays for single and multi-concentration screening of samples were replicated in three independent runs containing different passages of the cells (i.e., 3 independent biological replicates).

Cell Viability Assay

Cell viability assays were conducted in parallel with the RAIU assays to identify samples where a decrease in RAIU might be due to cytotoxicity. hNIS-HEK293T-EPA cells were seeded and grown in 96-well solid white assay plates (Corning, Corning, NY) and exposed to chemical samples as described for RAIU assay. CellTiter-Glo (Promega, Fitchburg, WI) reagent (70μL) was then added to each well and plates were shaken for 5 minutes at 700rpm. Plates were incubated at room temperature for 10 minutes and then read on a FLUOstar Omega plate reader (BMG Labtech, Cary, NC) using an endpoint luminescence protocol (top read) to measure relative light units (RLU) indicative of ATP concentration. Assays for multi-concentration screening of samples were

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replicated in three independent runs containing different passages of the cells (i.e., 3 independent biological replicates).

Chemical Screening

Chemicals were tested in a tiered approach to maximize resources and testing efficiency. Initial radioactive iodide uptake (RAIU) assays were performed as a single-concentration screen to identify active samples for subsequent testing in a concentration-response format. Each of the 310 blinded samples was tested at the maximum concentration (100μM, with some exceptions owing to solubility limits, see Table 2) in three independent RAIU assays using distinct passages of hNIS-HEK293T-EPA cells (i.e., bioreplicates). The median response for each sample from the three bioreplicates of the RAIU assays was used to determine whether the sample was active. Chemical samples were identified as active if the median RAIU inhibition was larger than a pre-determined activity threshold (20% in this study, refer to the data analysis section). Putative NIS inhibitors (i.e. active samples) were retested at six concentrations (obtained from 10-fold serial dilutions beginning with the maximum concentration, Table 2) in parallel RAIU and cell viability assays. The assay plate maps for single concentration screening and concentration-response assays are provided in Supplemental Figure 1.

Identification of Iodide Interference using Sandell-Kolthoff Reaction

Sandell-Kolthoff (SK) reaction is a colorimetric method to quantify iodide concentration through measurement of the iodide-catalyzed conversion of Ce^{4+} (yellow) to Ce^{3+} (colorless) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. SK reaction assay was used to detect the presence of

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iodide contamination or structural iodide in chemical samples that could possibly interfere with the RAIU assay and cause a false positive response. All 310 samples were tested by SK reaction following a previously developed protocol [ADDIN EN.CITE <EndNote><Cite><Author>Hallinger</Author><Year>2017</Year><RecNum>64</RecNum> <DisplayText>(Hallinger<style face="italic"> et al.</style>, 2017)</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798592">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hallinger, Daniel R.</author><author>Murr, Ashley S.</author><author>Buckalew, Angela R.</author><author>Simmons, Steven O.</author><author>Stoker, Tammy E.</author><author>Laws, Susan C.</author></authors></contributors><titles><title>Development of a screening approach to detect thyroid disrupting chemicals that inhibit the human sodium iodide symporter (NIS)</title><secondary-title>Toxicology in Vitro</secondary-title></titles><periodical><full-title>Toxicology in Vitro</full-title></periodical><pages>66-78</pages><volume>40</volume><keywords><keyword>Thyroid</keyword><keyword>Endo crine disruptors</keyword><keyword>Sodium iodide symporter</keyword><keyword>Chemical screening</keyword></keywords><dates><year>2017</year><pub-dates><date>4//</date></pub-dates></dates><isbn>0887-2333</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0887233316302569</url><url>http ://ac.els-cdn.com/S0887233316302569/1-s2.0-S0887233316302569-main.pdf?_tid=286edb04-

d8fa-11e6-b2db-

00000aacb360&acdnat=1484248141_9bcc422b76262b7c7843748a566dbb7c</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.tiv.2016.12.006</electronic-resource-num></record></Cite></EndNote>]. Briefly, 0.35μL of 100μM chemical samples were transferred to assay plate wells containing 69.7μL uptake buffer. Then standards (NaI, 100, 200, 300, 400, 500 nM) were added to specified duplicate wells at 70μL each. To initiate the reaction, 70μL of 24mM sodium arsenite solution and 70μL of 9.9 mM ammonium cerium sulfate solution was added to all wells. The reaction was incubated for 20 minutes at room temperature and subsequently measured for absorbance at 420nm on a SpectraMax Plus Microplate Reader (Molecular Devices, Sunnyvale, CA). Raw A_{420} readings were log10-transformed and NaI standards readings were fitted with linear regression to interpolate iodide concentration for each chemical. All testing was performed in triplicates.

Data analysis

Data analysis was performed in R (ver 3.3.0; R Foundation for Statistical Computing) and documented in R markdown (Supplemental File 1).

Single-concentration screening analysis

RAIU assay raw readings were measured as counts per minute (CPM) and normalized per 96-well plate as the percent activity of the median DMSO control CPM value (n = 12). The median of normalized percent activity from the 3 bioreplicates for each chemical was used to determine whether the chemical would be further evaluated in multi-concentration testing. The activity

threshold was set based on 3 times the baseline median absolute deviation (3bMAD) calculated using DMSO wells from all 15 assay plates in single-concentration screening. As 3bMAD was calculated to be 20.5%, the value for the activity inhibition threshold was rounded to 20% as a more conservative approach for moving chemicals forward to the multi-concentration RAIU and cell viability assays.

Multi-concentration screening analysis

Multi-concentration RAIU assay readings were expressed as CPM and cell viability assay readings were expressed as relative light unit (RLU). Both RAIU and cell viability assay raw readings were normalized using the same method employed in the single-concentration assay.

Dose-response curves were fitted using the Hill model provided in U.S. EPA's ToxCast Pipeline (tcpl v1.2.2) R package [ADDIN EN.CITE <EndNote><Cite><Author>Filer</Author><Year>2017</Year><RecNum>16</RecNum><DisplayText>(Filer<style face="italic"> et al.</style>, 2017)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1493134067">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Filer, Dayne L.</author><author>Kothiya, Parth</author><author>Setzer, R. Woodrow</author><author>Judson, Richard S.</author><author>Martin, Matthew T.</author></authors></contributors><titles><title>tcpl: the ToxCast pipeline for high-throughput screening data</title><secondary-title>Bioinformatics</secondary-title></titles><periodical><full-title>Bioinformatics</full-title></periodical><pages>618-

620</pages><volume>33</volume><number>4</number><dates><year>2017</year></dates><isbn>1367-4803</isbn><urls><related-urls><url>http://dx.doi.org/10.1093/bioinformatics/btw680</url></related-urls></urls><electronic-resource-num>10.1093/bioinformatics/btw680</electronic-resource-num></record></Cite></EndNote>]. The Hill model contains three parameters with bottom asymptote constrained to 0 and is given by the formula:

$$f(x,(tp,ga,gw)) = \frac{tp}{1+10^{(ga-x)gw}}$$

Where x is the log concentration, tp is the top asymptote for the given chemical, ga is the AC_{50} (the log concentration where the modeled activity equals 50% of the top asymptote), and gw is the Hill coefficient. The Hill model provided in the tcpl R package constrains the three parameters as following:

(1) $0 \leq tp \leq 1.2$ times the maximum response value

(2) (minimum log concentration minus 2) $\leq ga \leq$ (maximum log concentration plus 0.5)

(3) $0.3 \leq gw \leq 8$

Prior to curve fitting, the modeling function in the tcpl R package first checked for significant response by comparing the median of normalized chemical responses at each concentration to the 3bMAD value of each assay. The 3bMAD of the multi-concentration RAIU and cell viability assay (23.8% and 17.7% respectively) were calculated separately for each assay using the normalized

response values collected from the two lowest concentrations of all test chemical samples. Curve fitting was only performed when a significant response was present.

Prior to curve fitting, the normalized multi-concentration response data were inversed by using 100 minus the normalized value. This was done because the modeling function in the tcpl R package requires multi-concentration assay data to be conformed in the positive direction, whereas the RAIU and cell viability assay results were in the negative direction (inhibition from maximal response). Predicted response values (yhat) were calculated using the fitted Hill model parameters for each chemical. To visualize assay data and fitted dose-response curve together in the original negative direction, yhat values were subtracted by 100 and used to plot the dose-response curve. The normalized RAIU and cell viability responses, along with their fitted dose-response curve were plotted together in one graph for each chemical using the R package ggplot2 v2.2 [ADDIN EN.CITE <EndNote><Cite><Author>Wickham</Author><Year>2016</Year><RecNum>70</RecNum><DisplayText>(Wickham, 2016)</DisplayText><record><rec-number>70</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490799807">70</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>Wickham, Hadley</author></authors></contributors><titles><title>ggplot2: elegant graphics for data analysis</title></titles><dates><year>2016</year></dates><publisher>Springer</publisher><isbn>3319242776</isbn><urls></urls></record></Cite></EndNote>].

Calculation of Z', CV of DMSO, AC_{50}, $absEC_{50}$, Cytotox-point

To monitor the performance of the assay, quality control measures including Z' scores, coefficients of variation (CV) of DMSO, and AC_{50} of positive controls ($NaClO_4$ for RAIU, DCNQ for cell viability) were calculated by each 96-well assay plate. CV of DMSO was calculated by the equation: $CV = SD_{DMSO}/\mu_{DMSO}$, where SD_{DMSO} and μ_{DMSO} are the standard deviation and mean of the raw response value for DMSO control wells, respectively. Z' scores [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>1999</Year><RecNum>65</RecNum><DisplayText>(Zhang<style face="italic"> et al.</style>, 1999)</DisplayText><record><rec-number>65</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798592">65</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, Ji-Hu</author><author>Chung, Thomas D. Y.</author><author>Oldenburg, Kevin R.</author></authors></contributors><titles><title>A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays</title><secondary-title>Journal of Biomolecular Screening</secondary-title></titles><periodical><full-title>J Biomol Screen</full-title><abbr-1>Journal of biomolecular screening</abbr-1></periodical><pages>67-73</pages><volume>4</volume><number>2</number><dates><year>1999</year><pub-dates><date>1999/04/01</date></pub-dates></dates><publisher>SAGE Publications</publisher><isbn>1087-0571</isbn><urls><related-urls><url>http://journals.sagepub.com/doi/abs/10.1177/108705719900400206</url></related-urls></urls><electronic-resource-num>10.1177/108705719900400206</electronic-resource-num><access-date>2017/02/03</access-date></record></Cite></EndNote>] were calculated as:

$$Z' = 1 - \frac{3(\sigma_{pos} + \sigma_{DMSO})}{|\mu_{pos} - \mu_{DMSO}|}$$

Where σ_{pos} and μ_{pos} are the standard deviation and mean of normalized positive control ($NaClO_4$ for RAIU assay, DCNQ for cell viability assay) values at the highest 100 μM concentration. σ_{DMSO} and μ_{DMSO} are the standard deviation and mean of normalized DMSO control values. AC_{50} (the log concentration where the modeled activity equals 50% of the chemical's modeled maximal activity) was reported for all chemicals with fitted dose-response curves. For chemicals that inhibited iodide uptake by > 50%, absolute EC_{50} ($absEC_{50}$) were also reported. $absEC_{50}$ was determined as the log concentration where the modeled activity equals 50% of control activity. absEC80 was determined as the log concentration where the modeled activity equals 80% of control activity.

For chemicals that demonstrated significant cytotoxicity (exceeding 3bMAD of cell viability assay, 17.7%), the concentration where a significant reduction in cell viability for each chemical was determined and referred to as the cytotox-point. Cytotox-point is the equivalent of $absEC_{82.3}$, the log concentration where the modelled activity equals the significant cytotoxicity cutoff value (82.3% of control viability).

Chemical ranking score

To prioritize the chemicals for potential NIS inhibition activity, a new ranking system was developed based on two metrics that take into account the confounding impact of cytotoxicity on identifying RAIU inhibition activity: 1) toxicity-adjusted area (TAA) and 2) the difference of median responses of RAIU and cytotoxicity at maximum tested concentration (Median-Difference)

(Fig. 1). Ranking analysis was only performed if a chemical produced significant RAIU inhibition in multi-concentration screening. To obtain TAA (gray stripe area illustrated in Fig.1), RAIU inhibition area and cytotoxicity area were first calculated. RAIU inhibition area was defined by the RAIU 3bMAD (23.8%) significant threshold horizontal line (top border), maximum concentration vertical line (right border), and the RAIU dose-response curve. Cytotoxicity area was defined with the same top and right borders and the cell viability dose-response curve. TAA was then obtained by subtracting the cytotoxicity area from the RAIU inhibition area. Therefore, the numeric value of TAA is penalized when a chemical demonstrates strong cytotoxicity. Median-Difference was calculated using the median of cell viability responses minus the median of RAIU responses at the maximum tested concentration (usually 100 μM). Larger Median-Difference values represent larger separations between RAIU and cytotoxicity.

To rank test chemicals, the well-known NIS inhibitor $NaClO_4$ was chosen as the reference chemical to normalize the TAA and Median-Difference of each test chemical. Specifically, the TAA and Median-Difference values of $NaClO_4$ positive control included on each of the 54 multi-concentration testing plates were first calculated to obtain the median of $NaClO_4$ TAA and Median-Difference (150.03 and 95.67 respectively). The TAA and Median-Difference of test chemicals were normalized as the percentage of the median $NaClO_4$ TAA and Median-Difference separately and then summed to obtain a chemical ranking score. The ranking score of 200 represents the potency of the reference $NaClO_4$ (Fig. 1A). Fig. 1B, 1C and 1D show the dose-response of three test chemicals with lower level of ranking scores due to less RAIU inhibition and increased cytotoxicity level.

Results

Single-concentration screening

To facilitate the screening process, the 310 blinded samples were first tested in the RAIU assay at their maximum permissible concentration (typically at 100 μM, Table 2) to select potentially active compounds for concentration-response evaluation. Assay performance of single-concentration screening was monitored for each assay plate (total number of plates = 15) through CV of DMSO vehicle control, Z' and AC_{50} for the positive control chemical $NaClO_4$ (Table 3). The CV of DMSO control wells for each plate ranged from 4.91% to 11.04%, with mean ± SD of 7.14% ± 1.56%. Z' scores ranged from 0.65 to 0.84, with mean ± SD of 0.77 ± 0.05. AC_{50} (logM) of $NaClO_4$ ranged from -6.56 to -6.06, with mean ± SD of -6.44 ± 0.11. In addition, the responses of control chemicals included on each assay plate are summarized for the entire screening campaign in Table 4. The DMSO (vehicle control), 2,4-D (negative control), $NaNO_3$ (EC_{80} positive control), NaSCN (EC_{20} positive control) achieved mean ± SD of 100.63% ± 7.11%, 92.41% ± 4.24%, 81.25% ± 7.56%, 20.64% ± 1.12%, respectively. Overall, these metrics indicate the RAIU assay in single-concentration screening performed well with sufficient dynamic range, reproducibility, and reliability.

Single-concentration RAIU screening results for all 310 samples were ordered by increasing inhibitory median responses and plotted as median and maximum/minimum responses for each sample (Fig.2). These samples demonstrated a wide range of iodide uptake inhibition activity in the assay with median responses ranging from 2.8% to 116.6% of maximum iodide uptake relative

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to DMSO control. Of the 310 samples, 169 samples (54.5%) produced over the pre-determined 20% inhibition threshold and were selected for multi-concentration testing (Table 2).

Blinded internal replicate chemicals

The phase I_v2 chemical library consisted of 310 blinded samples that included 293 unique chemicals. Twelve of these chemicals were internally replicated (7 chemicals replicated twice and 5 chemicals replicated three times) to assess assay reproducibility. The robustness of the RAIU assay is shown in Fig. 3a, where all 12 replicated chemicals, excepting bisphenol A, produced highly reproducible results. Of the 12 replicated chemicals, 10 exceeded the 20% inhibition threshold and were subsequently tested in multi-concentration screening. The AC_{50} for each replicate of the 10 chemicals was calculated to assess the reproducibility of the RAIU assay in the multi-concentration setting (Fig. 3b, Supplemental Table 1). These 10 internal replicate samples had highly reproducible AC_{50} (logM) values with the maximum range of variation less than 0.25 (logM).

Multi-concentration testing

The 169 blinded samples with ≥20% inhibition in single-concentration RAIU screening were retested at 6 concentrations (0.001μM – 100μM) in parallel RAIU and cell viability assays. Both RAIU and cell viability assays performed reliably and their performance metrics calculated by each assay plate (total number of plates = 54) are summarized in Table 3. The CV of DMSO controls for RAIU and cell viability assays had mean ± SD of 8.61% ± 1.01%, 5.42% ± 1.47%, respectively. The Z' for the RAIU assay had a range of 0.64 - 0.78 and mean ± SD of 0.72 ± 0.03.

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The AC_{50} (logM) of positive controls ($NaClO_4$ for the RAIU assay, DCNQ for the cell viability assay) also demonstrated high reproducibility across assay plates, with mean ± SD of -6.38 ± 0.13, -4.83 ± 0.12 for RAIU and cell viability assays, respectively. The dose-response curves of $NaClO_4$ and DCNQ positive controls in multi-concentration screening are provided in Supplemental Figure 3. Additionally, the responses of all control chemicals are summarized across all assay plates in Table 4. All controls of the RAIU and cell viability assays showed great consistency with small variances in multi-concentration testing. The DMSO (vehicle control), 2,4-D (RAIU negative control), $NaNO_3$ (RAIU EC_{80} positive control), and NaSCN (RAIU EC_{20} positive control) achieved mean ± SD of 99.5% ± 8.28%, 90.86% ± 4.49%, 83.08% ± 7.17%, and 24.69% ± 2.71% respectively in RAIU assay. In the cell viability assay, DMSO, 2,4-D, $NaNO_3$, and NaSCN were inactive, with responses (mean±SD) of 100.92% ± 5.41%, 99.34% ± 3.21%, 98.95% ± 5.43%, and 104.3% ± 3.98%, respectively.

The significant activity threshold (3bMAD, calculated across all 54 assay plates in multi-concentration screening) for cell viability and RAIU assays were 17.7% and 23.8%, respectively. Among the 169 tested samples, 137 showed significant RAIU inhibition activity (>23.8% inhibition) and 127 exhibited significant cytotoxicity (>17.7% inhibition). Within the 137 samples with significant RAIU inhibition activity, 111 displayed a cytotoxic response while no change in cell viability was observed in 26 samples. There were 16 chemicals that caused significant cytotoxicity with no significant RAIU inhibition.

In reporting the RAIU and cell viability responses of each test chemical, several activity metrics, including AC_{50}, $absEC_{50}$, and cytotox-point (Table 2) were used together to aid in the interpretation of the assay results. AC_{50} and $absEC_{50}$ indicate the chemical potency from two different perspectives, as they differ in the inhibition activity level each represents. $absEC_{50}$ is the concentration that causes 50% inhibition, while AC_{50} is the concentration that triggers half-maximal inhibition, which is <50% inhibition for chemicals that do not fully inhibit NIS activity at the maximal concentration tested. AC_{50} is a useful metric to rank potencies even if the test chemical has low efficacy, provided that an activity curve can be fit. However, AC_{50} is not suitable to compare chemicals with different maximum inhibition activities, as their AC_{50} values represent the effective concentrations at different absolute activity levels. Moreover, the AC_{50} value of any given chemical may shift if it can produce stronger inhibition at higher test concentrations. To avoid these two issues, $absEC_{50}$ was calculated and reported. A reported $absEC_{50}$ value also indicates that the chemical exhibited ≥50% inhibition in the RAIU assay. For quick reference of the occurrence of cytotoxicity, the cytotox-point, which represents the concentration where significant cytotoxicity was observed, was reported along with the AC_{50} and $absEC_{50}$ values. Dose-response curves for each chemical are available in Supplemental Figure 2. AC50 and absEC50 values for cell viability assay are provided in Supplemental Table 2.

When comparing results from the highest concentration in multi-concentration screening and single-concentration screening, 87% of the chemicals (147 of 169) tested in multi-concentration format produced over 20% inhibition in RAIU assay, the significance threshold chosen for the single-concentration screening. Twenty-two chemicals failed to meet the 20% inhibition threshold

during multi-concentration testing. The range of their median RAIU inhibition in the initial single-concentration screen was between 20.9% to 51.8%, and 14 of the 22 chemicals had a median inhibition below 30%, indicating that these chemicals were weak actives in the initial single-concentration screen.

Chemical potency ranking

To prioritize chemicals for further analysis, the 169 samples tested in multi-concentration were further analyzed by a newly developed ranking system that estimates the RAIU inhibitory potency while mitigating the negative impact of cytotoxicity on identifying RAIU activity (Fig. 1). Of the 169 chemical samples tested in multi-concentration, 32 did not produce significant RAIU inhibition and hence were excluded in the ranking analysis. The ranking scores of the 137 chemical samples are listed and illustrated in Table 2 and Fig. 4. The TAA and Median-Difference values for these chemicals are provided in Supplemental Table 2.

In this study, the reference chemical $NaClO_4$ exhibited the most potent RAIU inhibition with a ranking score of 200 (both TAA and Median-Difference valued at 100). In comparison, the ranking score of the 137 test chemical samples ranged from 150.41 to -29.52, with 4 having ranking scores >100, 17 having ranking scores between 50 and 100, and 116 having ranking scores <50. An overview of the cytotoxicity of the ranked chemicals at the maximum concentration tested is shown in Fig. 4. Of the 137 chemical samples that produced significant RAIU inhibition, 27 exhibited no cytotoxicity, 67 exhibited significant but <50% cytotoxicity, and 43 exhibited >50% cytotoxicity at the maximum concentration.

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The dose-response curves along with the ranking score, AC_{50} and $absEC_{50}$ for the first 15 ranked samples (14 chemicals) are shown in Fig. 5a. These 15 samples have ranking score ranged from 150.41 to 64.10, AC50 ranged from -4.33 to -8.64, absEC50 ranged from -4.37 to -7.49. Fig. 5b shows three examples of the 32 chemicals that failed to produce significant RAIU inhibition, with either no significant or nominal cytotoxicity.

Identification of Iodide interference

The 310 samples were also tested with SK reactions to determine the presence of any contaminant iodide that may lead to potential false positive RAIU inhibition. Only two chemicals (iodosulfuron-methyl-sodium and 3-iodo-2-propynyl-N-butylcarbamate) produced positive SK reactions, suggesting that overall iodide contamination was not introducing false positive results in the RAIU assay. Iodosulfuron-methyl-sodium produced a positive SK reaction with interpolated content of 12.69 ± 1.12 pmol/well of equivalent I^-. However, this chemical had <20% RAIU inhibition in the single-concentration screening and therefore was not tested in the multi-concentration assay. 3-iodo-2-propynyl-N-butylcarbamate produced A_{420} readings beyond the upper range of the standard curve (> 35pmol/well). However, since 3-iodo-2-propynyl-N-butylcarbamate structurally contains iodide, it is unclear whether the strong S-K reaction was triggered by the chemical itself or the iodide contamination in the sample. This uncertainty about iodide contamination confounds any intrepetation of 3-iodo-2-propynyl-N-butylcarbamate results as an efficaious NIS inhibitor in the RAIU assay.

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Discussion

This study represents the first large-scale screening effort to identify potential NIS inhibitors in an environmental chemical library using our previously developed HTS approach [ADDIN EN.CITE <EndNote><Cite><Author>Hallinger</Author><Year>2017</Year><RecNum>64</RecNum><DisplayText>(Hallinger<style face="italic"> et al.</style>, 2017)</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1490798592">64</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hallinger, Daniel R.</author><author>Murr, Ashley S.</author><author>Buckalew, Angela R.</author><author>Simmons, Steven O.</author><author>Stoker, Tammy E.</author><author>Laws, Susan C.</author></authors></contributors><titles><title>Development of a screening approach to detect thyroid disrupting chemicals that inhibit the human sodium iodide symporter (NIS)</title><secondary-title>Toxicology in Vitro</secondary-title></titles><periodical><full-title>Toxicology in Vitro</full-title></periodical><pages>66-78</pages><volume>40</volume><keywords><keyword>Thyroid</keyword><keyword>Endocrine disruptors</keyword><keyword>Sodium iodide symporter</keyword><keyword>Chemical screening</keyword></keywords><dates><year>2017</year><pub-dates><date>4//</date></pub-dates></dates><isbn>0887-2333</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0887233316302569</url><url>http

://ac.els-cdn.com/S0887233316302569/1-s2.0-S0887233316302569-main.pdf?_tid=286edb04-d8fa-11e6-b2db-00000aacb360&acdnat=1484248141_9bcc422b76262b7c7843748a566dbb7c</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.tiv.2016.12.006</electronic-resource-num></record></Cite></EndNote>]. The results demonstrate that this assay performed with high reproducibility and reliability as measured by typical performance metrics for HTS assays. The assay demonstrated a high Z' score and low variability in DMSO vehicle controls in both the single- and multi-concentration RAIU screenings. The internal chemical replicates, included for quality control purposes, also demonstrated consistent responses that further support strong assay reproducibility.

Prioritizing chemical RAIU inhibition potency based on a cell-based assay can be confounded if the test compound exhibits strong cytotoxicity. Therefore, a great effort was made to conduct a parallel cell viability assay using the same batch of cell culture, the same treatment and experimental conditions with the RAIU assay to provide the best possible estimation of cytotoxicity. To maximize the usage of the rigorous cytotoxicity data, a novel potency ranking system was developed to prioritize potential NIS inhibitors. Based on both RAIU and cytotoxicity dose-responses, this system adapts cytotoxicity in calculating the two underlying metrics, TAA and Median-Difference. The ranking score was also normalized in reference to the well-known NIS inhibitor sodium perchlorate, making it compatible for comparisons with chemicals in future screenings. Overall, this ranking system enhances the quality of chemical prioritization when compared to other systems that rely on single point metrics. With this ranking system, the top

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ranked 15 samples (Fig. 5a) represent a diverse group of 14 environmental chemicals with different known toxicological properties and are further discussed below.

Several of these highly ranked chemicals are pesticides that showed potential effects on cellular energy. For example, etoxazole is an organofluorine acaricide-insecticide and was the highest ranked among all the tested chemicals, with a typical sigmoidal RAIU inhibition response and minimal cytotoxicity (25.2% median inhibition) at the highest test concentration. The U.S. EPA ToxRef database [ADDIN EN.CITE <EndNote><Cite><Author>Martin</Author><Year>2009</Year><RecNum>59</RecNum><DisplayText>(Martin<style face="italic"> et al.</style>, 2009)</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1499258815">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Martin, MT</author><author>Judson, RS</author><author>Reif, DM</author><author>Kavlock, RJ</author><author>Dix, DJ</author></authors></contributors><titles><title>Profiling chemicals based on chronic toxicity results from the US EPA ToxRef Database</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>392-399</pages><volume>117</volume><number>3</number><dates><year>2009</year></dates><isbn>0091-6765</isbn><urls></urls></record></Cite></EndNote>], a collection of curated *in vivo* regulatory toxicity information previously submitted to the agency, reveals that etoxazole can lead to increase of thyroid gland weight in both subchronic and chronic rat oral toxicity studies.

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Our finding is the first to show that etoxazole disrupts iodide uptake by NIS. However, whether etoxazole can directly interact with the NIS protein requires further investigation, as a study on the freshwater fish *Oreochromis niloticus* found that etoxazole exposure at high concentration can lead to increase of Na^+/K^+ ATPase activities in gill and muscle and a decrease of this activity in kidney [ADDIN EN.CITE <EndNote><Cite><Author>Üner</Author><Year>2005</Year><RecNum>42</RecNum><DisplayText>(Üner<style face="italic"> et al.</style>, 2005)</DisplayText><record><rec-number>42</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349898">42</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Üner, Nevin</author><author>Oruç, Elif</author><author>Sevgiler, Yusuf</author></authors></contributors><titles><title>Oxidative stress-related and ATPase effects of etoxazole in different tissues of Oreochromis niloticus</title><secondary-title>Environmental Toxicology and Pharmacology</secondary-title></titles><periodical><full-title>Environmental Toxicology and Pharmacology</full-title></periodical><pages>99-106</pages><volume>20</volume><number>1</number><keywords><keyword>Etoxazole</keyword><keyword>Antioxidant enzyme</keyword><keyword>Oxidative stress</keyword><keyword>Lipid peroxidation</keyword><keyword>ATPase</keyword><keyword>Fish tissues</keyword></keywords><dates><year>2005</year><pub-dates><date>7//</date></pub-dates></dates><isbn>1382-6689</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S1382668904002418</url><url>http

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://ac.els-cdn.com/S1382668904002418/1-s2.0-S1382668904002418-main.pdf?_tid=2d359ba4-39a4-11e7-8f97-00000aab0f26&acdnat=1494876475_48b693815708540978a9cf4a54820f14</url></related-urls></urls><electronic-resource-num>https://doi.org/10.1016/j.etap.2004.11.006</electronic-resource-num></record></Cite></EndNote>]. Since Na^+/K^+ ATPase maintains the critical cross-membrane sodium gradient necessary for NIS functionality, disruption of Na^+/K^+ ATPase activity can indirectly affect NIS activity. Another high-ranking chemical, niclosamide, may also have interfered with NIS function indirectly, as it is a pharmaceutical that uncouples oxidative phosphorylation in mitochondria [ADDIN EN.CITE <EndNote><Cite><Author>Pearson</Author><Year>1985</Year><RecNum>43</RecNum><DisplayText>(Pearson and Hewlett, 1985)</DisplayText><record><rec-number>43</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349898">43</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearson, R. D.</author><author>Hewlett, E. L.</author></authors></contributors><titles><title>NIclosamide therapy for tapeworm infections</title><secondary-title>Annals of Internal Medicine</secondary-title></titles><periodical><full-title>Annals of Internal Medicine</full-title></periodical><pages>550-551</pages><volume>102</volume><number>4</number><dates><year>1985</year></dates><isbn>0003-4819</isbn><urls><related-urls><url>http://dx.doi.org/10.7326/0003-4819-102-4-550</url></related-urls></urls><electronic-resource-num>10.7326/0003-4819-102-4-550</electronic-resource-num></record></Cite></EndNote>], thereby disrupt ATP production

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and hence Na^+/K^+ ATPase activity. To date, there is no report of niclosamide regarding thyroid toxicity, except its anti-proliferative effect in human thyroid cancer cells [ADDIN EN.CITE <EndNote><Cite><Author>Zhang</Author><Year>2012</Year><RecNum>44</RecNum><DisplayText>(Zhang<style face="italic"> et al.</style>, 2012)</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349899">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, Lisa</author><author>He, Mei</author><author>Zhang, Yaqin</author><author>Nilubol, Naris</author><author>Shen, Min</author><author>Kebebew, Electron</author></authors></contributors><titles><title>Quantitative High-Throughput Drug Screening Identifies Novel Classes of Drugs with Anticancer Activity in Thyroid Cancer Cells: Opportunities for Repurposing</title><secondary-title>The Journal of Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>The Journal of Clinical Endocrinology & Metabolism</full-title></periodical><pages>E319-E328</pages><volume>97</volume><number>3</number><dates><year>2012</year></dates><isbn>0021-972X</isbn><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2011-2671</url></related-urls></urls><electronic-resource-num>10.1210/jc.2011-2671</electronic-resource-num></record></Cite></EndNote>].

Several other insecticides in this study have been shown to disrupt energy metabolism and demonstrated similar atypical RAIU dose-response curves that may implicate an alternative mechanism of NIS inhibition. These chemicals include rotenone and pyridaben (Fig. 5a), which

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are both mitochondrial complex I inhibitors that disrupt electron transport leading to reduced ATP production [ADDIN EN.CITE <EndNote><Cite><Author>Hollingworth</Author><Year>1994</Year><RecNum>102</RecNum><DisplayText>(Hollingworth<style face="italic"> et al.</style>, 1994)</DisplayText><record><rec-number>102</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1496174640">102</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hollingworth, R. M.</author><author>Ahammadsahib, K. I.</author><author>Gadelhak, G.</author><author>McLaughlin, J. L.</author></authors></contributors><auth-address>PURDUE UNIV,DEPT MED CHEM & PHARMACOGNOSY,W LAFAYETTE,IN 47907.
HOLLINGWORTH, RM (reprint author), MICHIGAN STATE UNIV,PESTICIDE RES CTR,E LANSING,MI 48824, USA.</auth-address><titles><title>NEW INHIBITORS OF COMPLEX-I OF THE MITOCHONDRIAL ELECTRON-TRANSPORT CHAIN WITH ACTIVITY AS PESTICIDES</title><secondary-title>Biochemical Society Transactions</secondary-title><alt-title>Biochem. Soc. Trans.</alt-title></titles><periodical><full-title>Biochemical Society Transactions</full-title><abbr-1>Biochem. Soc. Trans.</abbr-1></periodical><alt-periodical><full-title>Biochemical Society Transactions</full-title><abbr-1>Biochem. Soc. Trans.</abbr-1></alt-periodical><pages>230-233</pages><volume>22</volume><number>1</number><keywords><keyword>NADH DEHYDROGENASE</keyword><keyword>REDUCTASE</keyword><keyword>ROTENONE</keyword><keyword>Biochemistry & Molecular

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Biology</keyword></keywords><dates><year>1994</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0300-5127</isbn><accession-num>WOS:A1994NA92900049</accession-num><work-type>Article; Proceedings Paper</work-type><urls><related-urls><url><Go to ISI>://WOS:A1994NA92900049</url></related-urls></urls><language>English</language></record></Cite></EndNote>]. Rotenone has been shown to inhibit iodide uptake in sheep thyroid slices [ADDIN EN.CITE <EndNote><Cite><Author>Tyler</Author><Year>1968</Year><RecNum>100</RecNum><DisplayText>(Tyler<style face="italic"> et al.</style>, 1968)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1496172914">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Tyler, D D</author><author>Gonze, Jeanine</author><author>Lamy, Françoise</author><author>Dumont, J. E.</author></authors></contributors><titles><title>Influence of mitochondrial inhibitors on the respiration and energy-dependent uptake of iodide by thyroid slices</title><secondary-title>Biochemical Journal</secondary-title></titles><periodical><full-title>Biochemical Journal</full-title></periodical><pages>123-133</pages><volume>106</volume><number>1</number><dates><year>1968</year></dates><urls></urls><electronic-resource-num>10.1042/bj1060123</electronic-resource-num></record></Cite></EndNote>] and pyridaben has been associated to reduced thyroid gland weight in subchronic rat study according to U.S.EPA ToxRef database [ADDIN EN.CITE

<EndNote><Cite><Author>Martin</Author><Year>2009</Year><RecNum>59</RecNum><DisplayText>(Martin<style face="italic"> et al.</style>, 2009)</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1499258815">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Martin, MT</author><author>Judson, RS</author><author>Reif, DM</author><author>Kavlock, RJ</author><author>Dix, DJ</author></authors></contributors><titles><title>Profiling chemicals based on chronic toxicity results from the US EPA ToxRef Database</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>392-399</pages><volume>117</volume><number>3</number><dates><year>2009</year></dates><isbn>0091-6765</isbn><urls></urls></record></Cite></EndNote>]. Several lower ranked chemicals (Supplemental Fig. 2) including fenpyroximate, tebufenpyrad (mitochondrial NADH-CoQ reductase inhibitor), and pyraclostrobin (quinone inhibitor) may also disrupt energy levels [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These chemicals have similar atypical dose-responses in the RAIU assay with a very flat slope and they all produced significant effects on cell viability. Since the Cell-Titer Glo viability assay quantifies ATP as an indicator of viable cells, this effect on cell viability could be the result of either energy metabolism disruption or cell death. A secondary cell viability assay using an alternative indicator of viability can confirm the cytotoxicity observed.

Several chemicals in the top 14 chemicals, including PFOS, triphenyltin hydroxide, and fipronil have been shown to disrupt thyroid function in previous studies and had significant effects on iodide uptake by NIS in the current study. Among these three chemicals, PFOS has been the most studied due to its widespread presence and persistence in the environment. PFOS was reported to decrease serum T4 levels in mammalian models such as the rat, mouse, and monkey [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aquatic exposure to PFOS has also been shown to increase T3 level, upregulate NIS expression, and alter expression of other HPT genes in zebrafish larvae [ADDIN EN.CITE <EndNote><Cite><Author>Shi</Author><Year>2009</Year><RecNum>53</RecNum><DisplayText>(Shi<style face="italic"> et al.</style>, 2009)</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349899">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Shi, Xiongjie</author><author>Liu, Chunsheng</author><author>Wu, Guoqiao</author><author>Zhou, Bingsheng</author></authors></contributors><titles><title>Waterborne exposure to PFOS causes disruption of the hypothalamus–pituitary–thyroid axis in zebrafish larvae</title><secondary-title>Chemosphere</secondary-title></titles><periodical><full-title>Chemosphere</full-title></periodical><pages>1010-1018</pages><volume>77</volume><number>7</number><keywords><keyword>PFOS</keyword><keyword>Hypothalamic–pituitary–thyroid axis</keyword><keyword>Thyroid hormone</keyword><keyword>Zebrafish</keyword></keywords><dates><year>2009</year><

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pub-dates><date>11//</date></pub-dates></dates><isbn>0045-6535</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0045653509009126</url></related-urls></urls><electronic-resource-num>https://doi.org/10.1016/j.chemosphere.2009.07.074</electronic-resource-num></record></Cite></EndNote>]. In addition, higher concentrations of serum PFOA and PFOS have been associated with current thyroid disease in the U.S. general adult population [ADDIN EN.CITE <EndNote><Cite><Author>Melzer</Author><Year>2010</Year><RecNum>54</RecNum><DisplayText>(Melzer<style face="italic"> et al.</style>, 2010)</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349899">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Melzer, David</author><author>Rice, Neil</author><author>Depledge, Michael H.</author><author>Henley, William E.</author><author>Galloway, Tamara S.</author></authors></contributors><titles><title>Association between Serum Perfluorooctanoic Acid (PFOA) and Thyroid Disease in the U.S. National Health and Nutrition Examination Survey</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>686-692</pages><volume>118</volume><number>5</number><dates><year>2010</year><pub-dates><date>01/20
10/17/received
01/07/accepted</date></pub-dates></dates><publisher>National Institute of Environmental Health

Sciences</publisher><isbn>0091-6765
1552-9924</isbn><accession-num>PMC2866686</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2866686/</url></related-urls></urls><electronic-resource-num>10.1289/ehp.0901584</electronic-resource-num><remote-database-name>PMC</remote-database-name></record></Cite></EndNote>]. In this study, the two PFOS samples (internally replicated in ToxCast library) both produced significant RAIU inhibition with similar dose-responses (Fig. 6a). The $absEC_{50}$ values for the two PFOS samples were also very close with values of -4.78 and -4.74 (logM), respectively. Triphenyltin hydroxide is a fungicide that has been shown to impair reproduction in rats and cause reduced pituitary, thyroid weight, and increased incidence of pituitary tumors [ADDIN EN.CITE <EndNote><Cite><Author>Golub</Author><Year>2004</Year><RecNum>55</RecNum><DisplayText>(Golub and Doherty, 2004)</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349899">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Golub, Mari S</author><author>Doherty, John D</author></authors></contributors><titles><title>Triphenyltin as a potential human endocrine disruptor</title><secondary-title>Journal of Toxicology and Environmental Health, Part B</secondary-title></titles><periodical><full-title>Journal of Toxicology and Environmental Health, Part B</full-title></periodical><pages>281-295</pages><volume>7</volume><number>4</number><dates><year>2004</year></dates><isbn>1093-7404</isbn><urls></urls></record></Cite></EndNote>]. A study with Japanese quail also reported decreased serum T4 level and impaired reproduction following triphenyltin

hydroxide dietary exposure [ADDIN EN.CITE <EndNote><Cite><Author>Grote</Author><Year>2006</Year><RecNum>56</RecNum><DisplayText>(Grote<style face="italic"> et al.</style>, 2006)</DisplayText><record><rec-number>56</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349899">56</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Grote, K.</author><author>Niemann, L.</author><author>Gericke, C.</author><author>Selzsam, B.</author><author>Chahoud, I.</author></authors></contributors><titles><title>Effects of fentin hydroxide on reproduction of the Japanese quail (Coturnix coturnix japonica)</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental Research</full-title></periodical><pages>81-88</pages><volume>101</volume><number>1</number><keywords><keyword>Fentin hydroxide</keyword><keyword>Organotin compounds</keyword><keyword>Japanese quail</keyword><keyword>Reproduction</keyword><keyword>Endorine disruption</keyword></keywords><dates><year>2006</year><pub-dates><date>5//</date></pub-dates></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935105001015</url></related-urls></urls><electronic-resource-num>https://doi.org/10.1016/j.envres.2005.07.004</electronic-resource-num></record></Cite></EndNote>]. In our study, triphenyltin hydroxide demonstrated a typical RAIU inhibition dose-response (absEC50 = -5.39 logM) with moderate cytotoxicity only at 100 μM. Fipronil is a broadly used insecticide that has been associated with elevated rates of T4

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elimination in the rat and increased hepatic enzyme activity was suggested to be the cause [ADDIN EN.CITE <EndNote><Cite><Author>Leghait</Author><Year>2009</Year><RecNum>57</RecNum><DisplayText>(Leghait<style face="italic"> et al.</style>, 2009)</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349900">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leghait, Julien</author><author>Gayrard, Véronique</author><author>Picard-Hagen, Nicole</author><author>Camp, Marion</author><author>Perdu, Elisabeth</author><author>Toutain, Pierre-Louis</author><author>Viguié, Catherine</author></authors></contributors><titles><title>Fipronil-induced disruption of thyroid function in rats is mediated by increased total and free thyroxine clearances concomitantly to increased activity of hepatic enzymes</title><secondary-title>Toxicology</secondary-title></titles><periodical><full-title>Toxicology</full-title></periodical><pages>38-44</pages><volume>255</volume><number>1–2</number><keywords><keyword>Thyroid disruptor</keyword><keyword>Rat</keyword><keyword>Clearance</keyword><keyword>UDPGT</keyword><keyword>Fipronil</keyword><keyword>5-Amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(trifluoromethylsulfinyl)-1H-pyrazole-3-carbonitrile</keyword></keywords><dates><year>2009</year><pub-dates><date>1/8/</date></pub-dates></dates><isbn>0300-483X</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0300483X08004654</url></related-urls></urls><electronic-resource-num>https://doi.org/10.1016/j.tox.2008.09.026</electronic-

resource-num></record></Cite></EndNote>]. The same group later conducted a fipronil study in sheep and found that the thyroid disruption activity previously observed in the rat could not be replicated in rams, and only a moderate level of increased T4 clearance was observed in ewes [ADDIN EN.CITE <EndNote><Cite><Author>Leghait</Author><Year>2010</Year><RecNum>58</RecNum><DisplayText>(Leghait<style face="italic"> et al.</style>, 2010)</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="09vdaavf8zzsfkefza7x90s6tasptssaefxe" timestamp="1496349900">58</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leghait, Julien</author><author>Gayrard, Véronique</author><author>Toutain, Pierre-Louis</author><author>Picard-Hagen, Nicole</author><author>Viguié, Catherine</author></authors></contributors><titles><title>Is the mechanisms of fipronil-induced thyroid disruption specific of the rat: Re-evaluation of fipronil thyroid toxicity in sheep?</title><secondary-title>Toxicology Letters</secondary-title></titles><periodical><full-title>Toxicology Letters</full-title></periodical><pages>51-57</pages><volume>194</volume><number>3</number><keywords><keyword>Fipronil</keyword><keyword>Thyroid toxicicity</keyword><keyword>Endocrine disruptor</keyword><keyword>Toxicokinetic</keyword><keyword>Sheep</keyword></keywords><dates><year>2010</year><pub-dates><date>5/4/</date></pub-dates></dates><isbn>0378-4274</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0378427410000329</url></related-urls></urls><electronic-resource-num>https://doi.org/10.1016/j.toxlet.2010.01.018</electronic-

resource-num></record></Cite></EndNote>]. In our study, fipronil demonstrated significant RAIU inhibition between 10 μM and 100 μM and significant cytotoxicity at 100 μM.

Apart from the chemicals discussed above, five of the top 14 chemicals were only associated with thyroid disruption activity in the U.S.EPA ToxRef database but no other published literature. The records in ToxRef database indicate that 3-iodo-2-propynyl-N-butylcarbamate, cyprodinil, and methoxyfenozide were associated with pathological changes in thyroid gland in subchronic rat toxicity studies. Cyprodinil also caused increased thyroid gland weight. ToxRef database also has records for captan and oxyfluorfen reporting increased thyroid gland weight in chronic rat toxicity studies. However, record usability in ToxRef for captan and oxyfluorfen was labaled as "deficient evaluation" and "unacceptable", respectively. Hence, these results may be unreliable. Fluroxypyr-meptyl and 2-(thiocyanomethylthio)benzothiazole were not previously associated with thyroid disruption, though similarly structured benzothiozoles have previously been identified as thyroid peroxidase inhibitors [ADDIN EN.CITE <EndNote><Cite><Author>Hornung</Author><Year>2015</Year><RecNum>91</RecNum><DisplayText>(Hornung<style face="italic"> et al.</style>, 2015)</DisplayText><record><rec-number>91</rec-number><foreign-keys><key app="EN" db-id="tsarvxesktrfvwe9d9rxsxthda0dev5r55ef" timestamp="1494528450">91</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hornung, Michael W.</author><author>Kosian, Patricia A.</author><author>Haselman, Jonathan T.</author><author>Korte, Joseph J.</author><author>Challis, Katie</author><author>Macherla,

Chitralekha</author><author>Nevalainen, Erica</author><author>Degitz, Sigmund J.</author></authors></contributors><titles><title>In Vitro, Ex Vivo, and In Vivo Determination of Thyroid Hormone Modulating Activity of Benzothiazoles</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>254-264</pages><volume>146</volume><number>2</number><dates><year>2015</year></dates><isbn>1096-6080</isbn><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kfv090</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfv090</electronic-resource-num></record></Cite></EndNote>].

The development and implementation of this approach to identify potential NIS inhibitors fills a critical gap in the capability to screen chemicals under the U.S.EPA's regulatory purview for thyroid disrupting activity. The findings reported here confirm that the cell-based screening approach can be effectively used to identify chemicals that directly compete with iodide for intracellular transport through the symporter, as well as those chemicals that alter NIS function by disruption of energy production required to maintain the sodium gradient. The use of a unique ranking system that incorporates the cytotoxicity response for each chemical provides a stronger foundation for further assessment of chemicals with commonalities in structural and toxicological properties and/or prioritization for further testing. Because of the likely alternative RAIU inhibition mechanisms among these chemicals, close examination of the dose-response is suggested rather than relying on a single metric such as the AC_{50} or $absEC_{50}$ to draw conclusions regarding NIS inhibition. In addition, as with most *in vitro* assays, chemical purity and solubility

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limitations need to be considered, warranting additional secondary assay testing to further confirm initial findings for high priority chemicals. For example, a secondary assay such as the rat thyroid FRTL-5 cell line based RAIU assay would add confidence to any HTS findings. Lastly, as with any *in vitro* assay, considerations of absorption, distribution, metabolism, excretion (ADME) as well as potential compensatory feedback are needed before assuming that a chemical would result in altered thyroid synthesis with exposure *in vivo*. Additional studies using short-term *in vivo* assays, such as those that employ amphibian or weanling rat models, are warranted to further investigate the thyroid-disruptive potential of NIS inhibitors.

As public concern increases over the effects of environmental chemicals on thyroid hormone signaling, there is an urgent need to expand the current knowledge base and understanding of the risks of thyroid disruption by a broader range of compounds. Iodide uptake into the thyroid via NIS is the critical initial step of thyroid hormone biosynthesis and is a known target of thyroid disruption in humans and wildlife. The screening of 293 ToxCast chemicals in the current study represents the first large scale effort to investigate NIS as a molecular target of environmental chemicals that cover a broad spectrum of structural and toxicological properties. The ranking of potential NIS inhibitors can inform the prioritization of chemicals for secondary testing. This ranking method will prove useful for the imminent screening of the ToxCast phase II and e1K chemical libraries for putative NIS inhibitors. Moreover, these data provide an integral component of the U.S.EPA's EDSP initiative to expand the coverage of known molecular targets of chemical-induced thyroid disruption (Noyes *et al.* 2017), as well as to support the development of a series of OECD test guidelines to assess chemicals for thyroid disrupting activity.

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Supplemental Data Description

Supplemental Figure 1: Assay plate map.

Supplemental Figure 2: Dose-response curves of all chemicals tested in multi-concentration

Supplemental Figure 3: Does-response curves of sodium perchlorate and DCNQ positive controls in multi-concentration screening

Supplemental Table 1: AC50s of the 10 internally replicated chemicals tested in multi-concentration

Supplemental Table 2： Chemical Potency Metrics Summary Table

Supplemental File 1: Documented Data Analysis in R

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This work was conducted at the National Health and Environmental Effects Research Laboratory (NHEERL), Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC. The authors gratefully acknowledge the contributions of Dr. Michael Hornung, Dr. William Munday and Dr. Katie Paul-Friedmann.

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Reference

[ADDIN EN.REFLIST]

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Abbreviations

EDSP21 (Endocrine Disruptor Screening Program in the 21st century), OECD (The Organization for Economic Co-operation and Development), ToxCast (Toxicity Forecaster), CV (coefficient of variation), NIS (sodium iodide symporter), RAIU (radioactive iodide uptake), RLU (relative light unit), SD (standard deviation), T_3 (triiodothyronine), T_4 (thyroxine), TH (thyroid hormone), 3bMAD (three times the baseline median absolute deviation), DMSO (dimethylsulfoxide), 2,4-D (2,4-dichlorophenoxyacetic acid), DCNQ (2,3-dichloro-1,4-napthoquinone), HEK (human embryonic kidney), AOP (adverse outcome pathway), HTS (high-throughput screening), DMEM (Dulbecco's Modified Eagle Medium), CPM (counts per minute), TAA (toxicity-adjusted area), PFOS (perfluorooctanesulfonic acid), PFOA (perfluorooctanoic acid)

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Figures

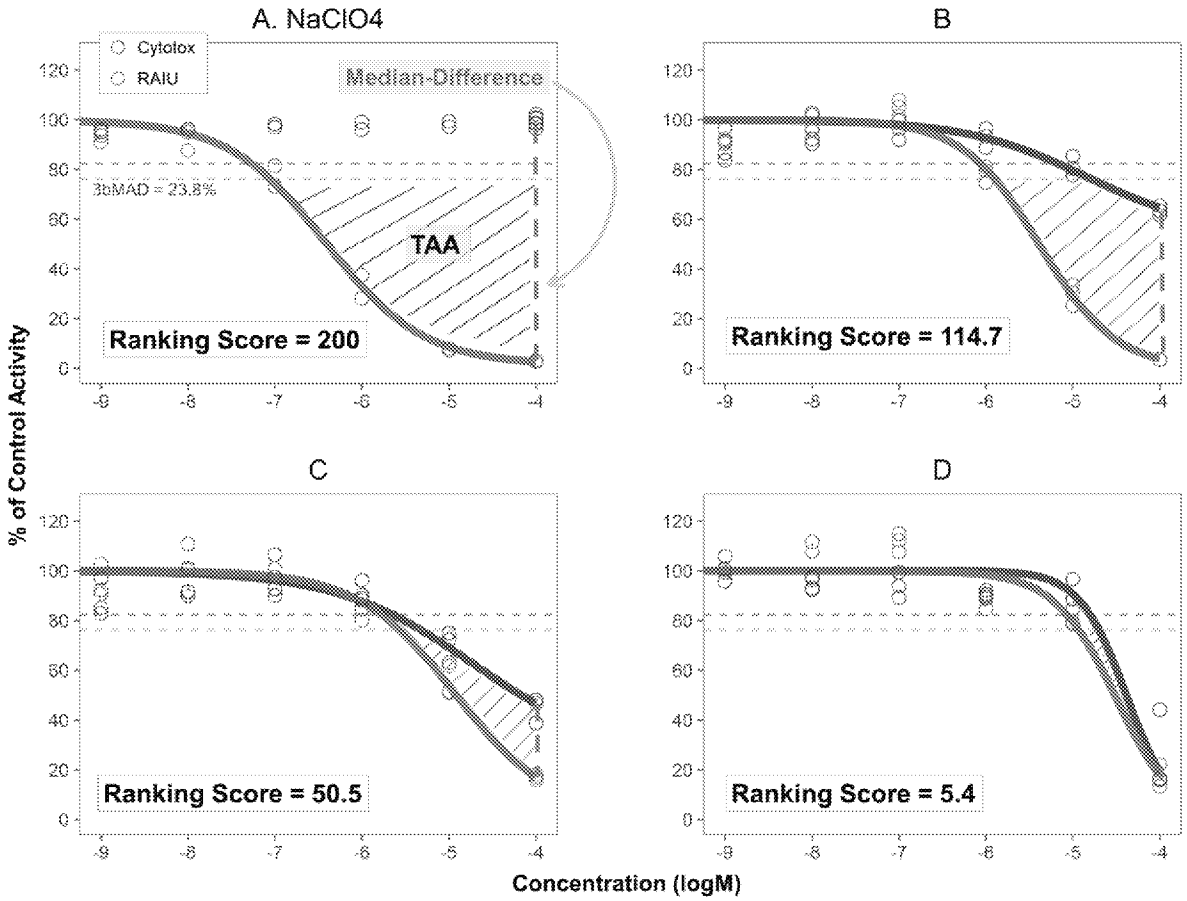

Fig. 1. Demonstration of ranking score, TAA and Median-Difference. Examples of chemical responses: A) sodium perchlorate, B) triphenyltin hydroxide, C) folpet, D) prodiamine. Cell viability and RAIU assay results are illustrated in red and blue respectively. The red and blue horizontal dotted lines represent the 3bMAD threshold for cell viability and RAIU assay respectively. Toxicity-adjusted area (TAA) is the gray striped area defined by 1) maximum concentration vertical line (right border), 2) the 3bMAD significant threshold horizontal line for RAIU assay (top border; blue dashed line), 3) the dose-response curve of RAIU and 4) if present,

the dose-response curve of cytotoxicity. The difference of median responses of RAIU and cytotoxicity at maximum tested concentration (Median-Difference) is indicated by the green vertical dotted line. Sodium perchlorate (A) was chosen as the reference NIS inhibitor to normalize test chemical TAA and Median-Difference as percentage values. Ranking score is obtained as the sum of normalized TAA and Median-Difference values. Therefore, sodium perchlorate has a ranking score of 200. B, C and D show three test chemicals with less RAIU inhibition and more cytotoxicity relative to sodium perchlorate. As the TAA and Median-Difference values decrease, their ranking scores also decrease.

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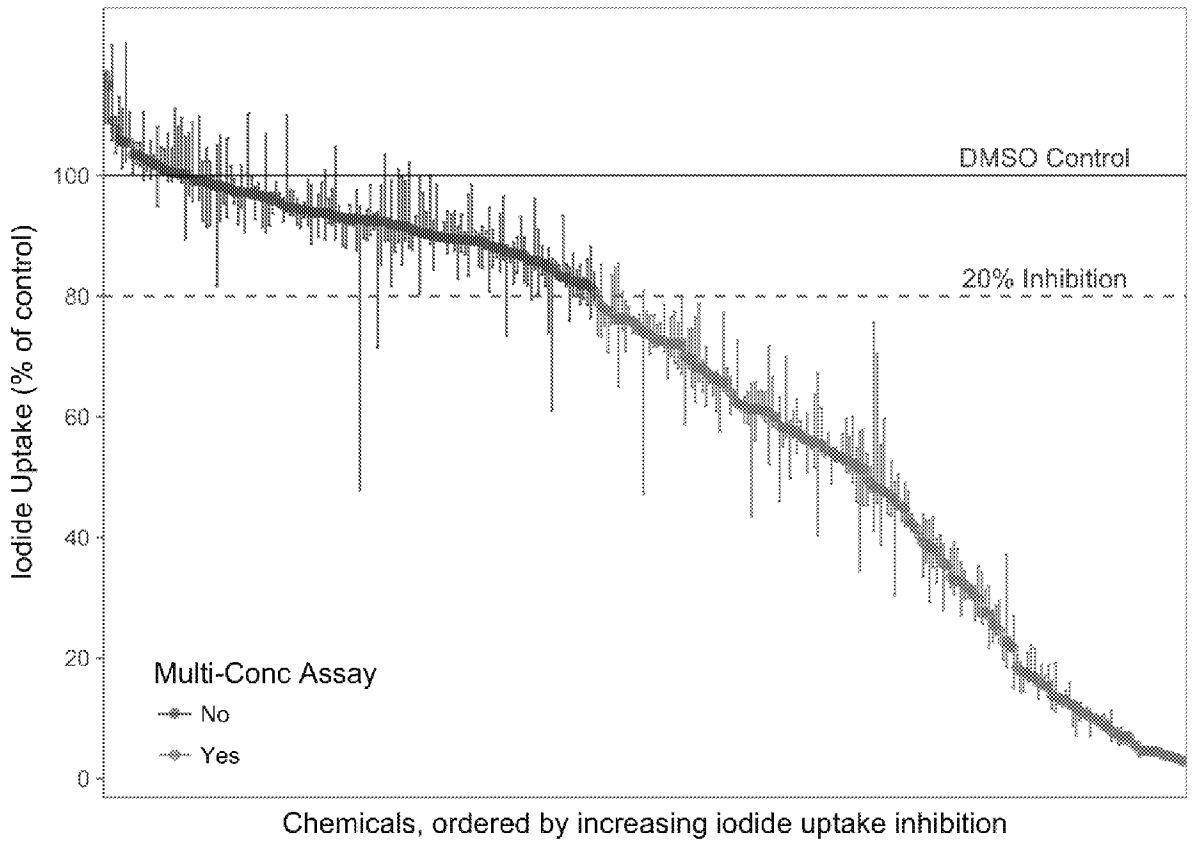
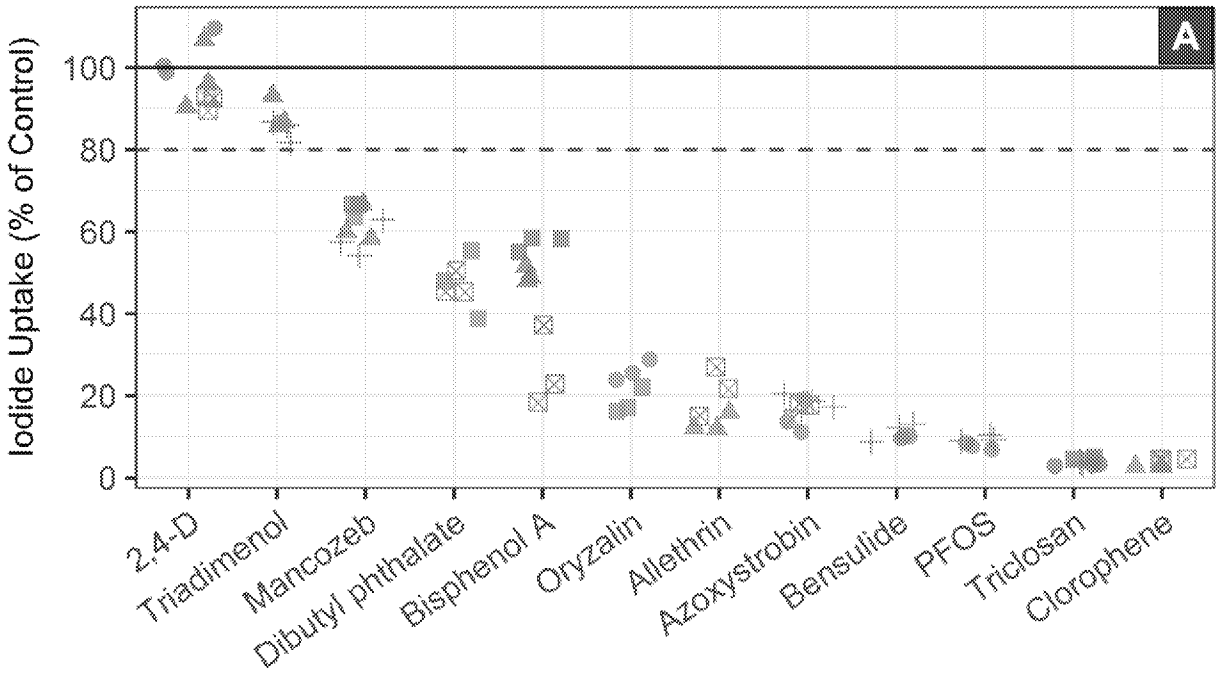


Fig. 2. Median and range of test chemical responses in single-concentration RAIU screening. Median response of each chemical is represented by the dot and vertical bar shows the maximal iodide uptake (top of the bar) and the minimum iodide uptake (bottom of the bar). The pink horizontal line represents the 20% inhibition threshold. 310 blinded samples were tested at maximum permissible concentrations (typically 100 μM). 169 chemicals (54.5%) were selected for multi-concentration testing based on a 20% inhibition activity threshold.


A
Iodide Uptake (% of Control)
100
80
60
40
20
0
2,4-D
Triadimenol
Mancozeb
Dibutyl phthalate
Bisphenol A
Oryzalin
Allethrin
Azoxystrobin
Bensulide
PFOS
Triclosan
Clorophene

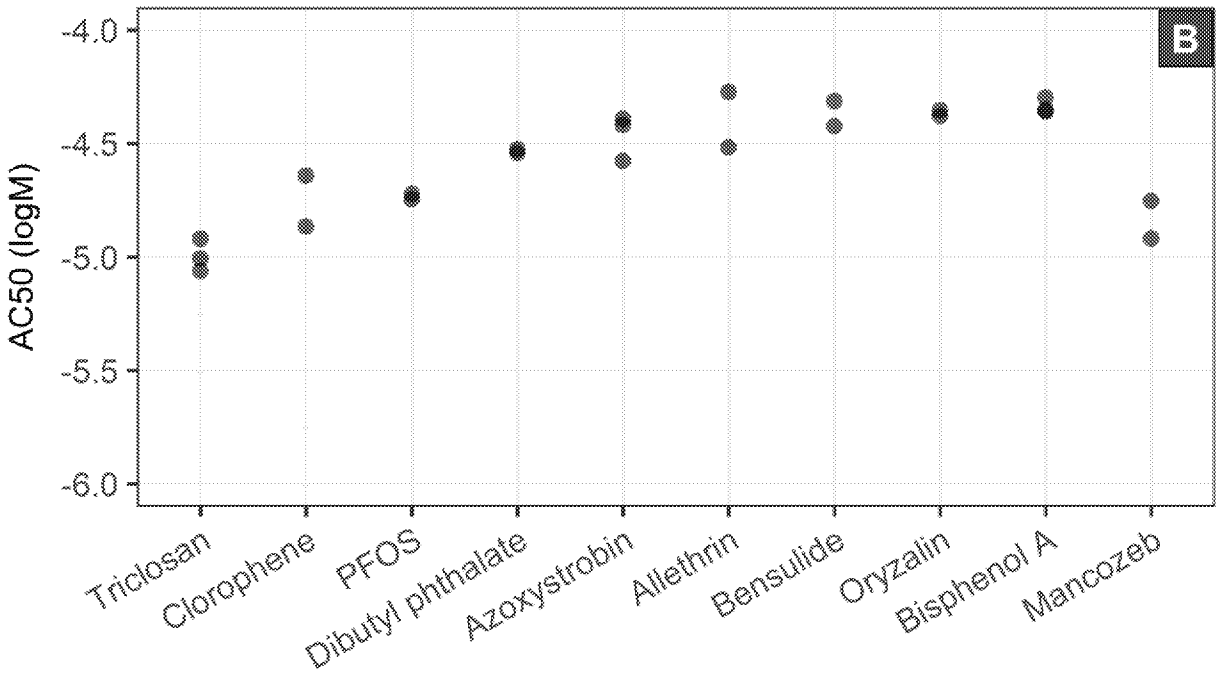

B
AC50 (logM)
-4.0
-4.5
-5.0
-5.5
-6.0
Triclosan
Clorophene
PFOS
Dibutyl phthalate
Azoxystrobin
Allethrin
Bensulide
Oryzalin
Bisphenol A
Mancozeb

Fig. 3. (A) Responses of internal replicates in single-concentration screening. 12 chemicals in the ToxCast phase1_v2 library were replicated 2 or 3 times (supplied in 2 or 3 blinded chemical samples). Colors represent different chemicals, while shapes indicate different internally replicated samples for a given chemical. Since each sample was tested in three bioreplicates, each shape for a given chemical has three data points. Ten of the 12 replicated chemicals that gave >20% inhibition (pink horizontal line) in this single-concentration test were subsequently tested in multi-concentration format (Fig. 3B). **(B) AC_{50} of internal replicates in multi-concentration screening.** Each symbol represents one AC50 value obtained from one sample of the chemical tested in three bioreplicates in multi-concentration.

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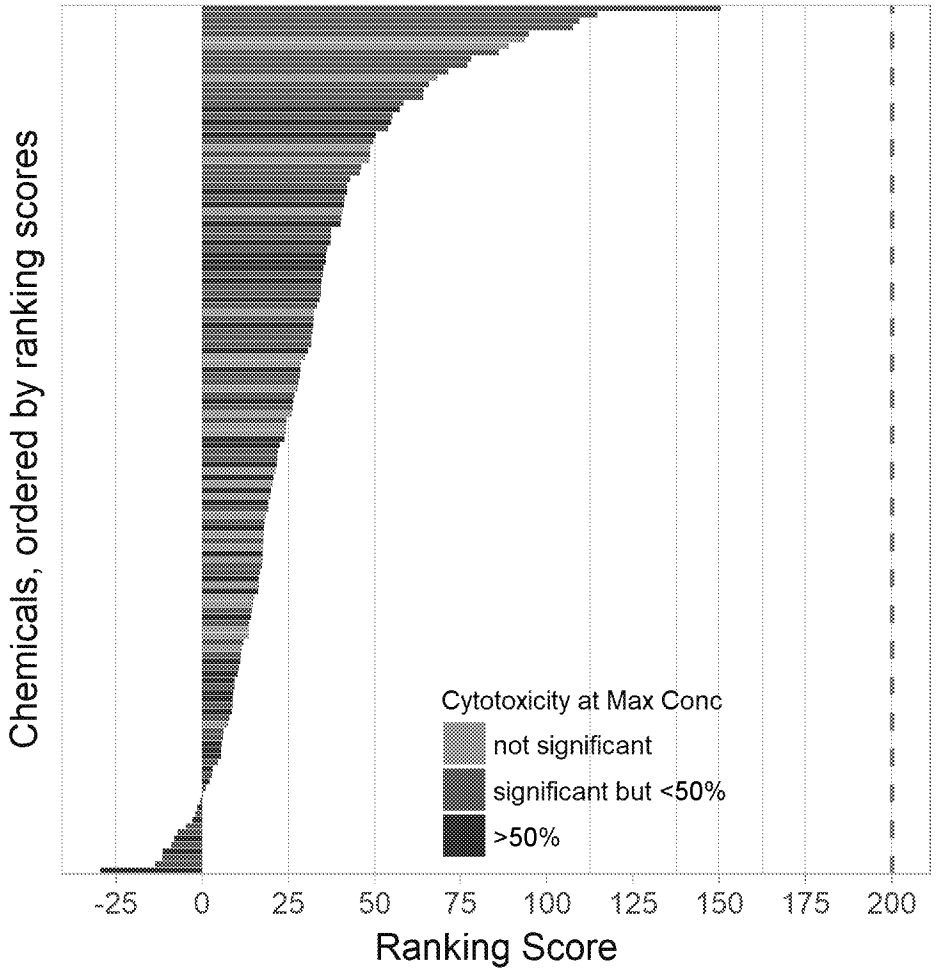

Fig. 4. Ranking scores for chemical samples tested in multi-concentration screening. Ranking scores were evaluated only if a chemical produced significant RAIU inhibition. Of the 169 chemical samples tested in multi-concentration, 32 did not show significant RAIU inhibition and were therefore excluded from the ranking analysis. The vertical dotted line is the ranking score of sodium perchlorate, which was used as the reference chemical in the ranking analysis. The ranking score of the 137 test chemical samples ranged from 150.41 to -29.52, with 4 having ranking score >100, 17 having ranking score between 50 and 100, and 116 having ranking score <50.

Cytotoxicity levels at the maximum testing concentration are indicated in colors shown. Of the 137 chemical samples that produced significant RAIU inhibition, 27 exhibited no cytotoxicity, 67 exhibited significant but <50% cytotoxicity, and 43 exhibited >50% cytotoxicity at the maximum concentration tested.

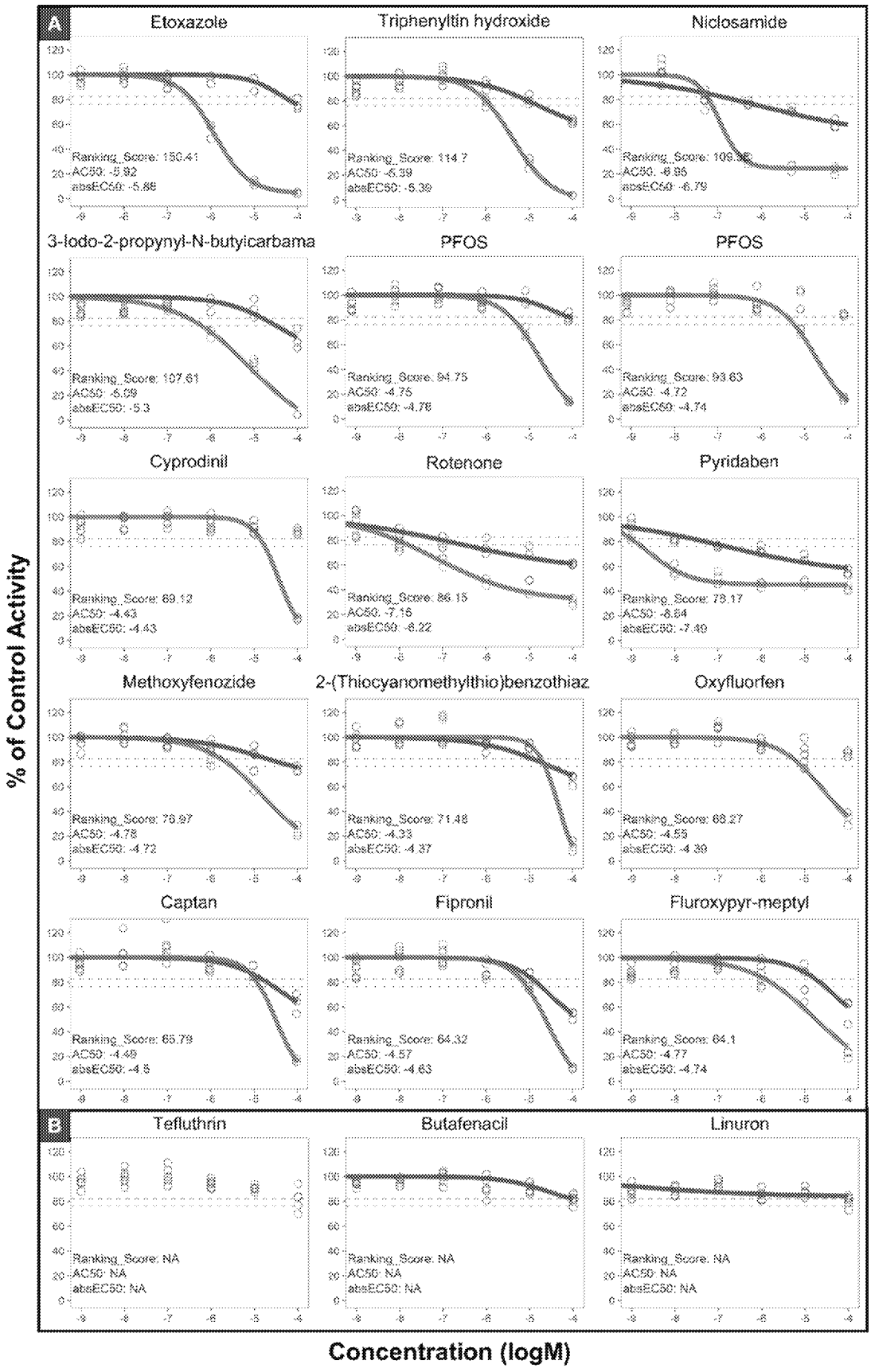
A
Etoxazole
Ranking_Score: 150.41
AC50: -5.92
absEC50: -5.88
Triphenyltin hydroxide
Ranking_Score: 114.7
AC50: -5.39
absEC50: -5.39
Niclosamide
Ranking_Score: 109.36
AC50: -6.85
absEC50: -6.79
3-Iodo-2-propynyl-N-butylcarbama
Ranking_Score: 107.61
AC50: -5.59
absEC50: -5.3
PFOS
Ranking_Score: 94.75
AC50: -4.75
absEC50: -4.78
PFOS
Ranking_Score: 93.63
AC50: -4.72
absEC50: -4.74
Cyprodinil
Ranking_Score: 69.12
AC50: -4.43
absEC50: -4.43
Rotenone
Ranking_Score: 86.15
AC50: -7.15
absEC50: -6.22
Pyridaben
Ranking_Score: 78.17
AC50: -8.64
absEC50: -7.49
Methoxyfenozide
Ranking_Score: 79.97
AC50: -4.78
absEC50: -4.72
2-(Thiocyanomethylthio)benzothiaz
Ranking_Score: 71.48
AC50: -4.33
absEC50: -4.37
Oxyfluorfen
Ranking_Score: 68.27
AC50: -4.55
absEC50: -4.39
Captan
Ranking_Score: 65.79
AC50: -4.49
absEC50: -4.5
Fipronil
Ranking_Score: 64.32
AC50: -4.57
absEC50: -4.63
Fluroxypyr-meptyl
Ranking_Score: 64.1
AC50: -4.77
absEC50: -4.74
B
Tefluthrin
Ranking_Score: NA
AC50: NA
absEC50: NA
Butafenacil
Ranking_Score: NA
AC50: NA
absEC50: NA
Linuron
Ranking_Score: NA
AC50: NA
absEC50: NA
% of Control Activity
Concentration (logM)

Fig. 5. Dose response, ranking score, AC50 and absEC50 of (A) top 15 ranked samples (14 chemicals) and (B) example chemicals that did not produce significant RAIU inhibition. Chemical responses (for three bioreplicates) are shown as circles with red representing cytotoxicity assay results and blue representing RAIU assay results. The red and blue horizontal dotted lines represent the 3bMAD threshold for cell viability and RAIU assay, respectively. AC_{50} and $absEC_{50}$ are expressed as logM.

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Tables

Table 1. Control chemicals included on each assay plate

Control Chemical	DMSO	2,4-D	DCNQ	NaClO4	$NaNO_3$	NaSCN
CAS No.	67-68-5	94-75-7	117-80-6	7601-89-0	7631-99-4	540-72-7
Purity (%)	99.9	98	98	98	99	98
Purpose	Vehicle control	Negative control	Cell viability assay, positive control	RAIU assay, positive control	RAIU assay, positive control (20% inhibition)	RAIU assay, positive control (80% inhibition)
Concentration (% or M)	0.5%	1E-4	1E-9, 1E-8, 1E-7, 1E-6, 1E-5, 1E-4	1E-9, 1E-8, 1E-7, 1E-6, 1E-5, 1E-4	1E-4	1E-4
Reps*/plate in Single-Con Screening	12	2	3 for 1E-4M, 1 for the rest	6 for 1E-4M, 2 for the rest	2	2
Reps*/plate in Multi-Con Screening	8	2	3 for 1E-4M, 1 for the rest	6 for 1E-4M, 2 for the rest	2	2

*Number of wells

Table 2. List of test chemicals and screening results

Max Conc: the maximum permissible concentration tested in single-concentration screening. Serial dilution of samples for multi-concentration assay started with this concentration.

*: precipitate visually observed in the well of stock chemical plate.

Hit call: indicates whether chemical median RAIU inhibition was over 20% in single-concentration screening. +: yes, -: no.

AC_{50}: the AC_{50} value derived from multi-concentration dose-response curve.

$absEC_{50}$: the $absEC_{50}$ value derived from multi-concentration dose-response curve if the maximum inhibition achieved by the chemical was over 50%.

Cytotox-point: the log concentration where the chemical started to show significant toxicity ($absEC_{82.3}$).

	Chemical	CAS NO.	Max Conc(M)	Hit Call	AC50	absEC50	Cytotox Point	Ranking Score
1	Etoxazole	153233-91-1	1.00E-04	+	-5.92	-5.88	-4.32	150.41
2	Triphenyltin hydroxide	76-87-9	1.00E-04	+	-5.39	-5.39	-5.17	114.70
3	Niclosamide	50-65-7	5.00E-05	+	-6.95	-6.79	-6.91	109.38
4	3-Iodo-2-propynyl-N-butylcarbamate	55406-53-6	1.00E-04	+	-5.09	-5.30	-4.80	107.61
5	PFOS	1763-23-1	8.00E-05	+	-4.75	-4.78	-4.09	94.75
6	PFOS	1763-23-1	8.00E-05	+	-4.72	-4.74	NA	93.63
7	Cyprodinil	121552-61-2	1.00E-04	+	-4.43	-4.43	NA	89.12
8	Rotenone	83-79-4	1.00E-04	+	-7.15	-6.22	-7.30	86.15
9	Pyridaben	96489-71-3	1.00E-04	+	-8.64	-7.49	-7.60	78.17
10	Methoxyfenozide	161050-58-4	1.00E-04	+	-4.78	-4.72	-4.68	76.97
11	2-(Thiocyanomethylthio)benzothiazole	21564-17-0	1.00E-04	+	-4.33	-4.37	-4.91	71.48
12	Oxyfluorfen	42874-03-3	1.00E-04	+	-4.55	-4.39	NA	68.27
13	Captan	133-06-2	9.50E-05	+	-4.49	-4.50	-4.81	65.79
14	Fipronil	120068-37-3	1.00E-04	+	-4.57	-4.63	-4.92	64.32
15	Fluroxypyr-meptyl	81406-37-3	1.00E-04	+	-4.77	-4.74	-4.74	64.10
16	Cyhalofop-butyl	122008-85-9	9.50E-05	+	-5.47	-4.75	-5.07	58.47
17	Fenpyroximate (Z,E)	111812-58-9	1.00E-04	+	-6.79	-6.07	-7.09	57.34
18	Thiobencarb	28249-77-6	1.00E-04	+	-4.38	-4.34	-4.70	55.20
19	Emamectin benzoate	155569-91-8	1.00E-04	+	-4.88	-4.99	-5.18	54.82
20	Diphenylamine	122-39-4	1.00E-04	+	-4.74	-4.28	-5.59	54.01
21	Folpet	133-07-3	1.00E-04	+	-4.93	-4.92	-5.65	50.48
22	Endosulfan	115-29-7	1.00E-04	+	-4.35	-4.39	-4.92	49.72
23	Prometryn	7287-19-6	1.00E-04	+	-4.44	NA	NA	48.73
24	Zoxamide	156052-68-5	1.00E-04	+	-4.48	-4.37	-4.66	48.72
25	Cyazofamid	120116-88-3	1.00E-04	+	-5.59	NA	NA	48.49
26	Parathion	56-38-2	1.00E-04	+	-4.72	-4.49	-4.01	46.24
27	Fenthion	55-38-9	1.00E-04	+	-4.40	-4.18	-3.72	45.87
28	Mancozeb	8018-01-7	5.00E-05	+	-4.92	NA	-4.80	43.00
29	Bifenazate	149877-41-8	1.00E-04	+	-4.42	-4.39	-4.87	42.05

30	Clorophene	120-32-1	1.00E-04	+	-4.87	-5.07	-4.68	41.98
31	Trifloxystrobin	141517-21-7	1.00E-04	+	-5.67	-5.05	-5.99	41.32
32	Triclosan	3380-34-5	1.00E-04	+	-5.01	-5.00	-4.98	41.22
33	Methoxychlor	72-43-5	9.50E-05	+	-4.58	NA	NA	40.75
34	Quinoxyfen	124495-18-7	1.00E-04	+	-4.47	-4.44	-4.85	40.43
35	Triflumizole	68694-11-1	1.00E-04	+	-4.53	-4.61	-4.82	40.28
36	Prallethrin	23031-36-9	9.50E-05	+	-4.38	-4.33	-4.66	37.48
37	S-Bioallethrin	28434-00-6	1.00E-04	+	-4.42	-4.37	-4.62	37.39
38	Coumaphos	56-72-4	1.00E-04	+	-5.00	-4.79	-4.95	37.24
39	Chlorpyrifos-methyl	5598-13-0	1.00E-04	+	-5.01	NA	-5.16	36.26
40	Fluoxastrobin	361377-29-9	1.00E-04	+	-4.95	-4.84	-5.63	35.85
41	Triclosan	3380-34-5	1.00E-04	+	-5.06	-5.11	-5.13	35.85
42	Pyraclostrobin	175013-18-0	1.00E-04	+	-6.02	-5.91	-6.27	35.19
43	Fenoxaprop-ethyl	66441-23-4	1.00E-04	+	-4.53	-4.09	-5.05	35.03
44	Fenoxycarb	72490-01-8	1.00E-04	+	-4.47	-4.51	-4.91	34.58
45	Hexaconazole	79983-71-4	1.00E-04	+	-4.45	-4.13	-4.55	34.50
46	Diclosulam	145701-21-9	1.00E-04	+	-4.82	NA	-4.92	34.38
47	Clorophene	120-32-1	1.00E-04	+	-4.64	-4.75	-4.69	34.14
48	Tebupirimfos	96182-53-5	1.00E-04	+	-4.61	-4.42	-4.54	33.31
49	Abamectin	71751-41-2	1.00E-04*	+	-4.33	NA	NA	32.50
50	Pyriproxyfen	95737-68-1	1.00E-04	+	-4.70	-4.11	-4.90	32.40
51	Triclosan	3380-34-5	1.00E-04	+	-4.92	-4.90	-5.01	32.32
52	Carfentrazone-ethyl	128639-02-1	1.00E-04	+	-4.35	-4.03	-4.40	31.97
53	Pirimiphos-methyl	29232-93-7	1.00E-04	+	-4.43	NA	-4.18	31.71
54	Dibutyl phthalate	84-74-2	1.00E-04	+	-4.54	NA	-3.98	31.65
55	Methylene bis(thiocyanate)	6317-18-6	1.00E-04	+	-4.66	-4.79	-4.86	30.68
56	Bisphenol A	80-05-7	1.00E-04	+	-4.36	NA	NA	29.86
57	Dithiopyr	97886-45-8	9.50E-05	+	-4.65	NA	NA	28.75
58	Tebufenpyrad	119168-77-3	1.00E-04	+	-5.60	-5.82	-6.21	28.57
59	Diclofop-methyl	51338-27-3	1.00E-04	+	-4.49	-4.12	-4.51	28.35
60	Dibutyl phthalate	84-74-2	1.00E-04	+	-4.53	NA	-4.29	28.05
61	Lactofen	77501-63-4	1.00E-04	+	-4.79	NA	NA	27.70
62	Piperonyl butoxide	51-03-6	1.00E-04	+	-4.22	NA	-4.87	26.83
63	Buprofezin	69327-76-0	1.00E-04	+	-4.55	-4.61	-4.95	26.43
64	Cloprop	101-10-0	1.00E-04	+	-4.49	NA	-3.45	26.25
65	Flutolanil	66332-96-5	1.00E-04	+	-4.50	NA	NA	25.91
66	Cinmethylin	87818-31-3	1.00E-04	+	-4.23	NA	-4.43	24.38
67	Chlorpropham	101-21-3	1.00E-04	+	-4.42	NA	NA	24.33
68	Clodinafop-propargyl	105512-06-9	1.00E-04	+	-5.70	NA	NA	24.25
69	Phosalone	2310-17-0	1.00E-04	+	-4.46	-4.35	-4.59	23.91
70	Allethrin	584-79-2	1.00E-04	+	-4.52	-4.49	-4.82	22.64
71	Disulfoton	298-04-4	1.00E-04	+	-4.27	NA	-4.44	21.93
72	Flumiclorac-pentyl	87546-18-7	1.00E-04	+	-4.50	-4.16	-5.26	21.87
73	Forchlorfenuron	68157-60-8	1.00E-04	+	-4.44	-4.50	-4.94	21.64
74	Flumetralin	62924-70-3	1.00E-04	+	-4.33	NA	NA	21.33
75	Ethalfluralin	55283-68-6	1.00E-04	+	-5.16	-4.93	-5.93	20.66
76	Lindane	58-89-9	1.00E-04	+	-4.32	NA	NA	20.50
77	Fluazinam	79622-59-6	9.00E-05	+	-5.16	-5.13	-5.40	20.06
78	Cyfluthrin	68359-37-5	1.00E-04	+	-4.57	NA	NA	19.87
79	Tri-allate	2303-17-5	1.00E-04	+	-4.61	-4.57	-4.84	19.20
80	Imazalil	35554-44-0	1.00E-04	+	-4.50	NA	-4.94	19.16
81	Cypermethrin	52315-07-8	1.00E-04	+	-4.96	NA	NA	18.48
82	Amitraz	33089-61-1	1.00E-04	+	-4.22	NA	-4.94	18.15
83	Tetraconazole	112281-77-3	9.50E-05	+	-4.65	-4.33	-4.86	18.01
84	Thiazopyr	117718-60-2	1.00E-04	+	-4.62	NA	NA	17.88
85	Trifluralin	1582-09-8	1.00E-04	+	-4.95	NA	-5.61	17.76
86	Tebufenozide	112410-23-8	1.00E-04	+	-4.68	NA	NA	17.75

87	Azoxystrobin	131860-33-8	1.00E-04	+	-4.58	-4.59	-5.04	17.64
88	Mancozeb	8018-01-7	5.00E-05	+	-4.75	NA	NA	17.52
89	Fluazifop-butyl	69806-50-4	1.00E-04	+	-4.36	NA	-4.26	17.41
90	Fenarimol	60168-88-9	1.00E-04	+	-5.11	NA	-1.70	16.84
91	Allethrin	584-79-2	1.00E-04	+	-4.27	-4.24	-4.69	16.46
92	Maneb	12427-38-2	1.00E-04	+	-4.37	NA	NA	16.39
93	Flusilazole	85509-19-9	1.00E-04	+	-4.25	-4.16	-4.66	16.20
94	Bisphenol A	80-05-7	1.00E-04	+	-4.35	NA	NA	15.20
95	Ametryn	834-12-8	1.00E-04	+	-4.26	NA	NA	14.78
96	Fluazifop-P-butyl	79241-46-6	1.00E-04	+	-4.41	NA	-4.84	14.47
97	Diniconazole	83657-24-3	1.00E-04	+	-4.50	-4.56	-4.79	14.21
98	Pendimethalin	40487-42-1	1.00E-04	+	-4.32	NA	-4.36	13.68
99	Fenitrothion	122-14-5	1.00E-04	+	-4.49	NA	NA	13.48
100	Isazofos	42509-80-8	1.00E-04	+	-4.26	NA	NA	13.45
101	Oxadiazon	19666-30-9	1.00E-04	+	-4.30	NA	-4.43	12.04
102	Hexythiazox	78587-05-0	1.00E-04	+	-4.46	NA	NA	11.36
103	Fenamidone	161326-34-7	1.00E-04	+	-4.29	NA	-4.09	11.25
104	Difenoconazole	119446-68-3	1.00E-04	+	-4.75	-4.90	-5.09	11.04
105	Fluthiacet-methyl	117337-19-6	1.00E-04	+	-4.72	NA	-3.59	10.68
106	Azoxystrobin	131860-33-8	1.00E-04	+	-4.42	-4.47	-5.06	10.24
107	Oryzalin	19044-88-3	1.00E-04	+	-4.38	-4.17	-4.63	9.45
108	Thidiazuron	51707-55-2	1.00E-04	+	-4.44	NA	-4.23	9.43
109	Famoxadone	131807-57-3	1.00E-04	+	-5.69	-4.81	-6.04	8.99
110	Dicofol	115-32-2	1.00E-04	+	-4.54	-4.61	-4.72	8.89
111	Propargite	2312-35-8	1.00E-04	+	-4.40	NA	-4.64	8.80
112	2,2-Bis(4-hydroxyphenyl)-1,1,1-trichloroethane	2971-36-0	1.00E-04	+	-4.39	-4.46	-4.90	8.69
113	Propiconazole	60207-90-1	1.00E-04	+	-4.39	NA	-4.75	7.91
114	Chlorethoxyfos	54593-83-8	1.00E-04	+	-4.41	NA	NA	7.53
115	Thiodicarb	59669-26-0	1.00E-04	+	-4.91	NA	-4.83	6.17
116	Ethofumesate	26225-79-6	1.00E-04	+	-4.52	NA	-4.56	6.01
117	Bensulide	741-58-2	1.00E-04	+	-4.42	-4.43	-4.83	5.59
118	Prodiamine	29091-21-2	1.00E-04	+	-4.49	-4.52	-4.80	5.44
119	Bensulide	741-58-2	1.00E-04	+	-4.31	-4.34	-4.72	5.44
120	Bisphenol A	80-05-7	1.00E-04	+	-4.30	NA	-3.77	4.51
121	Flumioxazin	103361-09-7	1.00E-04	+	-4.38	-4.40	-4.84	3.04
122	Methidathion	950-37-8	1.00E-04	+	-4.42	NA	-4.22	2.81
123	Azoxystrobin	131860-33-8	1.00E-04	+	-4.39	-4.39	-5.02	2.15
124	Butralin	33629-47-9	1.00E-04	+	-4.35	NA	-4.67	1.05
125	Dicloran	99-30-9	1.00E-04	+	-4.63	NA	-5.03	0.28
126	Oryzalin	19044-88-3	1.00E-04	+	-4.35	NA	-4.60	-0.65
127	Fenbuconazole	114369-43-6	1.00E-04	+	-4.27	-4.30	-4.72	-1.43
128	Thiram	137-26-8	1.00E-04	+	-4.18	-4.04	-4.88	-2.03
129	Tetramethrin	7696-12-0	1.00E-04	+	-4.41	-4.32	-4.88	-2.91
130	Profenofos	41198-08-7	5.00E-05	+	-4.55	NA	-4.90	-4.66
131	Quizalofop-ethyl	76578-14-8	8.50E-05	+	-4.42	NA	-4.65	-7.22
132	Prochloraz	67747-09-5	1.00E-04	+	-4.18	-4.12	-4.69	-8.05
133	Milbemectin (mixture of 70% Milbemcin A4, 30% Milbemycin A3)	NOCAS_34742	9.50E-05	+	-4.22	NA	-5.04	-8.94
134	Captafol	2425-06-1	1.00E-04	+	-4.45	-4.49	-5.06	-11.37
135	Tribufos	78-48-8	1.00E-04	+	-4.94	NA	-5.22	-11.50
136	Benfluralin	1861-40-1	1.00E-04	+	-4.62	NA	-4.78	-13.71
137	MGK-264	113-48-4	1.00E-04	+	-4.28	NA	-4.73	-29.52
138	Chlorothalonil	1897-45-6	1.00E-04	+	NA	NA	-4.03	NA
139	Propanil	709-98-8	1.00E-04	+	NA	NA	-3.88	NA
140	Bromoxynil	1689-84-5	8.00E-05	+	NA	NA	-5.22	NA

141	Napropamide	15299-99-7	1.00E-04	+	NA	NA	NA	NA
142	Nitrapyrin	1929-82-4	1.00E-04	+	NA	NA	NA	NA
143	Propetamphos	31218-83-4	1.00E-04	+	NA	NA	NA	NA
144	Myclobutanil	88671-89-0	1.00E-04	+	NA	NA	NA	NA
145	Malathion	121-75-5	1.00E-04	+	NA	NA	-4.32	NA
146	Resmethrin	10453-86-8	1.00E-04	+	NA	NA	-4.41	NA
147	Fenpropathrin	39515-41-8	1.00E-04	+	NA	NA	NA	NA
148	Picloram	1918-02-1	1.00E-04	+	NA	NA	NA	NA
149	Fludioxonil	131341-86-1	1.00E-04	+	NA	NA	-4.17	NA
150	Acibenzolar-S-methyl	135158-54-2	1.00E-04	+	NA	NA	NA	NA
151	Azinphos-methyl	86-50-0	1.00E-04	+	NA	NA	-3.99	NA
152	Mancozeb	8018-01-7	5.00E-05	+	NA	NA	NA	NA
153	Boscalid	188425-85-6	1.00E-04	+	NA	NA	-3.30	NA
154	Butachlor	23184-66-9	1.00E-04	+	NA	NA	-4.37	NA
155	Tefluthrin	79538-32-2	1.00E-04	+	NA	NA	NA	NA
156	Butafenacil	134605-64-4	1.00E-04	+	NA	NA	-4.04	NA
157	Tralkoxydim	87820-88-0	1.00E-04	+	NA	NA	NA	NA
158	Pyraflufen-ethyl	129630-19-9	1.00E-04	+	NA	NA	-4.33	NA
159	Prometon	1610-18-0	1.00E-04	+	NA	NA	NA	NA
160	Vinclozolin	50471-44-8	1.00E-04	+	NA	NA	NA	NA
161	2-Phenylphenol	90-43-7	1.00E-04	+	NA	NA	NA	NA
162	Clomazone	81777-89-1	1.00E-04	+	NA	NA	NA	NA
163	Flufenpyr-ethyl	188489-07-8	1.00E-04	+	NA	NA	NA	NA
164	Chlorpyrifos oxon	5598-15-2	9.50E-05	+	NA	NA	-4.01	NA
165	Fenhexamid	126833-17-8	1.00E-04	+	NA	NA	-4.15	NA
166	Cycloate	1134-23-2	1.00E-04	+	NA	NA	NA	NA
167	Naled	300-76-5	1.00E-04	+	NA	NA	NA	NA
168	Linuron	330-55-2	1.00E-04	+	NA	NA	NA	NA
169	EPTC	759-94-4	1.00E-04	+	NA	NA	NA	NA
170	Bifenthrin	82657-04-3	1.00E-04	-	NA	NA	NA	NA
171	Bentazone	25057-89-0	1.00E-04	-	NA	NA	NA	NA
172	Mesotrione	104206-82-8	1.00E-04	-	NA	NA	NA	NA
173	Esfenvalerate	66230-04-4	1.00E-04	-	NA	NA	NA	NA
174	Thiophanate-methyl	23564-05-8	1.00E-04	-	NA	NA	NA	NA
175	Trichlorfon	52-68-6	1.00E-04	-	NA	NA	NA	NA
176	Carbaryl	63-25-2	1.00E-04	-	NA	NA	NA	NA
177	2,4-Dichlorophenoxyacetic acid	94-75-7	1.00E-04	-	NA	NA	NA	NA
178	Boric acid	10043-35-3	1.00E-04	-	NA	NA	NA	NA
179	Dichlorprop	120-36-5	1.00E-04	-	NA	NA	NA	NA
180	Dicrotophos	141-66-2	1.00E-04	-	NA	NA	NA	NA
181	Butylate	2008-41-5	1.00E-04	-	NA	NA	NA	NA
182	Dimethylarsinic acid	75-60-5	1.00E-04	-	NA	NA	NA	NA
183	Dichlorvos	62-73-7	5.00E-05	-	NA	NA	NA	NA
184	Malaoxon	1634-78-2	1.00E-04	-	NA	NA	NA	NA
185	Cyanazine	21725-46-2	1.00E-04	-	NA	NA	NA	NA
186	Methomyl	16752-77-5	1.00E-04	-	NA	NA	NA	NA
187	PFOA	335-67-1	1.00E-04	-	NA	NA	NA	NA
188	Propoxur	114-26-1	1.00E-04	-	NA	NA	NA	NA
189	Imazethapyr	81335-77-5	1.00E-04	-	NA	NA	NA	NA
190	Imidacloprid	138261-41-3	1.00E-04	-	NA	NA	NA	NA
191	Fenamiphos	22224-92-6	1.00E-04	-	NA	NA	NA	NA
192	Clopyralid	1702-17-6	1.00E-04	-	NA	NA	NA	NA
193	Metalaxyl	57837-19-1	1.00E-04	-	NA	NA	NA	NA
194	Monocrotophos	6923-22-4	1.00E-04	-	NA	NA	NA	NA
195	Indoxacarb	173584-44-6	8.00E-05	-	NA	NA	NA	NA
196	Acephate	30560-19-1	1.00E-04	-	NA	NA	NA	NA
197	Anilazine	101-05-3	1.00E-04*	-	NA	NA	NA	NA

198	Diuron	330-54-1	1.00E-04	-	NA	NA	NA	NA
199	Clofentezine	74115-24-5	1.00E-04*	-	NA	NA	NA	NA
200	Methamidophos	10265-92-6	1.00E-04	-	NA	NA	NA	NA
201	Thiamethoxam	153719-23-4	1.00E-04	-	NA	NA	NA	NA
202	Formetanate hydrochloride	23422-53-9	1.00E-04	-	NA	NA	NA	NA
203	Fluometuron	2164-17-2	1.00E-04	-	NA	NA	NA	NA
204	Difenzoquat metilsulfate	43222-48-6	1.00E-04	-	NA	NA	NA	NA
205	Bendiocarb	22781-23-3	1.00E-04	-	NA	NA	NA	NA
206	Alachlor	15972-60-8	1.00E-04	-	NA	NA	NA	NA
207	Dimethenamid	87674-68-8	1.00E-04	-	NA	NA	NA	NA
208	2,4-Dichlorophenoxyacetic acid	94-75-7	1.00E-04	-	NA	NA	NA	NA
209	Ethylene thiourea	96-45-7	1.00E-04	-	NA	NA	NA	NA
210	Azamethiphos	35575-96-3	1.00E-04	-	NA	NA	NA	NA
211	Dazomet	533-74-4	1.00E-04	-	NA	NA	NA	NA
212	Pyrimethanil	53112-28-0	1.00E-04	-	NA	NA	NA	NA
213	Propyzamide	23950-58-5	1.00E-04	-	NA	NA	NA	NA
214	Triadimenol	55219-65-3	1.00E-04	-	NA	NA	NA	NA
215	Pirimicarb	23103-98-2	1.00E-04	-	NA	NA	NA	NA
216	Isoxaben	82558-50-7	1.00E-04	-	NA	NA	NA	NA
217	Acetochlor	34256-82-1	1.00E-04	-	NA	NA	NA	NA
218	Acifluorfen	50594-66-6	1.00E-04	-	NA	NA	NA	NA
219	Tepraloxydim	149979-41-9	1.00E-04	-	NA	NA	NA	NA
220	Clopyralid-olamine	57754-85-5	1.00E-04	-	NA	NA	NA	NA
221	2,4-DB	94-82-6	1.00E-04	-	NA	NA	NA	NA
222	Hexazinone	51235-04-2	1.00E-04	-	NA	NA	NA	NA
223	Tebuthiuron	34014-18-1	1.00E-04	-	NA	NA	NA	NA
224	Iprodione	36734-19-7	1.00E-04	-	NA	NA	NA	NA
225	Dicamba	1918-00-9	1.00E-04	-	NA	NA	NA	NA
226	Methyl parathion	298-00-0	1.00E-04	-	NA	NA	NA	NA
227	Fluroxypyr	69377-81-7	1.00E-04	-	NA	NA	NA	NA
228	Dimethomorph	110488-70-5	1.00E-04	-	NA	NA	NA	NA
229	Benomyl	17804-35-2	1.00E-04	-	NA	NA	NA	NA
230	Monomethyl phthalate	4376-18-5	1.00E-04	-	NA	NA	NA	NA
231	Diazinon	333-41-5	1.00E-04	-	NA	NA	NA	NA
232	Cyclanilide	113136-77-9	1.00E-04	-	NA	NA	NA	NA
233	Cyanamide	420-04-2	1.00E-04	-	NA	NA	NA	NA
234	Ethoprop	13194-48-4	1.00E-04	-	NA	NA	NA	NA
235	Penoxsulam	219714-96-2	1.00E-04*	-	NA	NA	NA	NA
236	Clothianidin	210880-92-5	1.00E-04	-	NA	NA	NA	NA
237	Di(2-ethylhexyl) phthalate	117-81-7	1.00E-04	-	NA	NA	NA	NA
238	Acetamiprid	135410-20-7	1.00E-04	-	NA	NA	NA	NA
239	Novaluron	116714-46-6	1.00E-04*	-	NA	NA	NA	NA
240	Isoxaflutole	141112-29-0	1.00E-04	-	NA	NA	NA	NA
241	Imazamox	114311-32-9	1.00E-04	-	NA	NA	NA	NA
242	Sulfentrazone	122836-35-5	1.00E-04	-	NA	NA	NA	NA
243	Cyproconazole	94361-06-5	9.50E-05	-	NA	NA	NA	NA
244	Pymetrozine	123312-89-0	1.00E-04	-	NA	NA	NA	NA
245	Spiroxamine	118134-30-8	1.00E-04	-	NA	NA	NA	NA
246	Quinclorac	84087-01-4	1.00E-04	-	NA	NA	NA	NA
247	Triclopyr	55335-06-3	1.00E-04	-	NA	NA	NA	NA
248	Propamocarb hydrochloride	25606-41-1	1.00E-04	-	NA	NA	NA	NA
249	Monobutyl phthalate	131-70-4	1.00E-04	-	NA	NA	NA	NA
250	Pentachloronitrobenzene	82-68-8	1.00E-04	-	NA	NA	NA	NA
251	Flufenacet	142459-58-3	1.00E-04	-	NA	NA	NA	NA
252	Imazapyr	81334-34-1	1.00E-04	-	NA	NA	NA	NA
253	Trifloxysulfuron-sodium	199119-58-9	1.00E-04*	-	NA	NA	NA	NA
254	Propazine	139-40-2	1.00E-04	-	NA	NA	NA	NA

255	Thiacloprid	111988-49-9	1.00E-04	-	NA	NA	NA	NA
256	2-Methoxyethanol	109-86-4	1.00E-04	-	NA	NA	NA	NA
257	Chloridazon	1698-60-8	1.00E-04	-	NA	NA	NA	NA
258	Asulam	3337-71-1	1.00E-04	-	NA	NA	NA	NA
259	Pyrithiobac-sodium	123343-16-8	1.00E-04	-	NA	NA	NA	NA
260	Deisopropylatrazine	1007-28-9	1.00E-04	-	NA	NA	NA	NA
261	Molinate	2212-67-1	1.00E-04	-	NA	NA	NA	NA
262	Oxytetracycline dihydrate	6153-64-6	1.00E-04	-	NA	NA	NA	NA
263	Spirodiclofen	148477-71-8	1.00E-04	-	NA	NA	NA	NA
264	Carboxin	5234-68-4	1.00E-04	-	NA	NA	NA	NA
265	Oxamyl	23135-22-0	1.00E-04	-	NA	NA	NA	NA
266	Symclosene	87-90-1	1.00E-04	-	NA	NA	NA	NA
267	Fosthiazate	98886-44-3	1.00E-04	-	NA	NA	NA	NA
268	Sethoxydim	74051-80-2	1.00E-04	-	NA	NA	NA	NA
269	Dimethoate	60-51-5	1.00E-04	-	NA	NA	NA	NA
270	MCPA	94-74-6	1.00E-04	-	NA	NA	NA	NA
271	Paclobutrazol	76738-62-0	1.00E-04	-	NA	NA	NA	NA
272	Dipropyl 2,5-pyridinedicarboxylate	136-45-8	1.00E-04	-	NA	NA	NA	NA
273	Methyl isothiocyanate	556-61-6	1.00E-04	-	NA	NA	NA	NA
274	DEET	134-62-3	1.00E-04	-	NA	NA	NA	NA
275	Cyromazine	66215-27-8	1.00E-04	-	NA	NA	NA	NA
276	Imazaquin	81335-37-7	1.00E-04	-	NA	NA	NA	NA
277	Metribuzin	21087-64-9	1.00E-04	-	NA	NA	NA	NA
278	Flumetsulam	98967-40-9	1.00E-04	-	NA	NA	NA	NA
279	Triadimefon	43121-43-3	1.00E-04	-	NA	NA	NA	NA
280	Metolachlor	51218-45-2	1.00E-04	-	NA	NA	NA	NA
281	Permethrin	52645-53-1	1.00E-04	-	NA	NA	NA	NA
282	Terbacil	5902-51-2	1.00E-04	-	NA	NA	NA	NA
283	Triadimenol	55219-65-3	1.00E-04	-	NA	NA	NA	NA
284	Etridiazole	2593-15-9	1.00E-04	-	NA	NA	NA	NA
285	Propoxycarbazone-sodium	181274-15-7	1.00E-04	-	NA	NA	NA	NA
286	Mevinphos	7786-34-7	1.00E-04	-	NA	NA	NA	NA
287	Bromacil	314-40-9	1.00E-04	-	NA	NA	NA	NA
288	Metam-sodium hydrate	6734-80-1	1.00E-04	-	NA	NA	NA	NA
289	2,4-Dichlorophenoxyacetic acid	94-75-7	1.00E-04	-	NA	NA	NA	NA
290	Thiabendazole	148-79-8	1.00E-04	-	NA	NA	NA	NA
291	Atrazine	1912-24-9	1.00E-04	-	NA	NA	NA	NA
292	2-Phenoxyethanol	122-99-6	1.00E-04	-	NA	NA	NA	NA
293	Icaridin	119515-38-7	1.00E-04	-	NA	NA	NA	NA
294	Imazapic	104098-48-8	1.00E-04	-	NA	NA	NA	NA
295	Aldicarb	116-06-3	1.00E-04	-	NA	NA	NA	NA
296	Triticonazole	131983-72-7	9.50E-05	-	NA	NA	NA	NA
297	Diazoxon	962-58-3	1.00E-04	-	NA	NA	NA	NA
298	Maleic hydrazide	123-33-1	1.00E-04	-	NA	NA	NA	NA
299	Daminozide	1596-84-5	1.00E-04	-	NA	NA	NA	NA
300	Mepiquat chloride	24307-26-4	1.00E-04	-	NA	NA	NA	NA
301	Norflurazon	27314-13-2	1.00E-04	-	NA	NA	NA	NA
302	Chloroneb	2675-77-6	1.00E-04	-	NA	NA	NA	NA
303	Ethephon	16672-87-0	1.00E-04	-	NA	NA	NA	NA
304	Iodosulfuron-methyl-sodium	144550-36-7	1.00E-04	-	NA	NA	NA	NA
305	Simazine	122-34-9	1.00E-04	-	NA	NA	NA	NA
306	MEHP	4376-20-9	1.00E-04	-	NA	NA	NA	NA
307	Cymoxanil	57966-95-7	1.00E-04	-	NA	NA	NA	NA
308	Diquat dibromide monohydrate	6385-62-2	5.00E-05	-	NA	NA	NA	NA
309	Dimethyl phthalate	131-11-3	1.00E-04	-	NA	NA	NA	NA
310	Dichlobenil	1194-65-6	1.00E-04	-	NA	NA	NA	NA

Table 3. Summary of assay performance metrics for single-concentration and multi-concentration screening.

Assay[1]	CV of DMSO		Z' Score		AC50 of positive control[2]	
	mean±SD	range	mean±SD	range	mean±SD	range
Single-con RAIU	7.14% ± 1.56%	4.91% - 11.04%	0.77 ± 0.05	0.65 - 0.84	-6.44 ± 0.11	-6.56 - -6.06
Multi-con RAIU	8.61% ± 1.01%	6.70 - 11.50	0.72 ± 0.03	0.64 - 0.78	-6.38 ± 0.13	-6.57 - -6.04
Multi-con Cell Viability	5.42% ± 1.47%	2.80 - 9.53	n.a.	n.a.	-4.83 ± 0.12	-4.92 - -4.47

1: All metrics were calculated per assay plate (single-con: n=15, multi-con: n=54) and summarized separately for single-concentration and multi-concentration screenings.

2: AC50 of positive controls were calculated from the dose-responses of $NaClO_4$ and DCNQ for RAIU and cell viability assay respectively. Unit: logM.

n.a.: unable to calculate.

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Table 4. Summary of normalized responses of control chemicals across all plates

Assay[1]	DMSO	2,4-D	DCNQ[2] (1E-4M)	$NaClO_4$[2] (1E-4M)	$NaNO_3$	NaSCN
single-con RAIU	100.63 ± 7.11	92.41 ± 4.24	n.a.	2.85 ± 0.36	81.25 ± 7.56	20.64 ± 1.12
multi-con RAIU	99.5 ± 8.28	90.86 ± 4.49	3.92 ± 3.37	3.28 ± 0.38	83.08 ± 7.17	24.69 ± 2.71
multi-con Cell Viability	100.92 ± 5.41	99.34 ± 3.21	3.72 ± 0.38	99.19 ± 4.69	98.95 ± 5.43	104.3 ± 3.98

Mean ± S.D.

n.a.: not available as DCNQ was not included in the single-concentration screening.

1. Data were calculated by collecting normalized response for each chemical from all assay plates. Values represent the percent of control activity. 2,4-D, $NaNO_3$, and NaSCN were at a concentration of 100 μM.

2. For DCNQ and $NaClO_4$, though they were included on each assay plate in six concentrations, only the responses from 100 μM concentration are summarized in this table.

September, 2016

NHEERL Fact Sheet

High-Throughput Screening of ToxCast Phase I Chemical Library for Sodium Iodide Symporter (NIS) Inhibitors

To be submitted to *Toxicological Sciences*

Jun Wang[1,2], Daniel R. Hallinger[1], Ashley S. Murr[1], Angela R. Buckalew[1], Steven O. Simmons[3], Tammy E. Stoker[1], and Susan C. Laws.[1]

[1]Endocrine Toxicology Branch, Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory, ORD, U.S.EPA, Research Triangle Park, NC.
[2]Oak Ridge Institute for Science and Education, US Dept. of Energy, Oak Ridge, TN 37831.
[3]National Center for Computational Toxicology, ORD, U.S.EPA, Research Triangle Park, NC.

Relevant National Research Program project/area of research: This paper supports Chemical Safety for Sustainability (CSS) research on High Throughput Toxicology, CSS 16.01, Task 2.1, *Development and optimization of vitro assays to address EDSP chemical activity toward targets affecting thyroid hormone,* Milestone 2. *Development of a Thyroid Sodium Iodide Symporter (NIS) Assay.*

Impact Statement: A novel screening approach has been developed to rapidly identify chemicals that can inhibit the uptake of iodide by the thyroid and disrupt the synthesis of thyroid hormones. This work addressed an urgent need and request from the Office of Coordination and Science Policy to develop *in vitro* assays to detect potential thyroid toxicants, and now provides a rapid screening approach that targets a key molecular initiating event, the uptake of iodide as mediated by the thyroid sodium iodide symporter (NIS), within the thyroid hormone pathway. This assay was used to screen the ToxCast Phase 1 chemical library. These findings for the Phase1-v2 chemicals can be utilized during an upcoming 2018 FIFRA Science Advisory Panel review to obtain recommendations and feedback for the Agency's Endocrine Disrupting Screening Program regarding the appropriate use of high throughput in vitro assays for the thyroid hormone pathway. This work is also of international interest because of the novel cell line created for this RAIU assay and its potential use for the development of an OECD test guideline.

Background: The Agency's Endocrine Disruptor Screening Program in the 21st century (EDSP21) aims to use high-throughput and computational toxicology methods to screen and prioritize chemicals for further testing based on their potential to affect estrogen, androgen, and thyroid pathways ([HYPERLINK "https://www.epa.gov/endocrine-disruption"]). The EDSP21 is currently limited in the ability to screen for chemicals that have the potential to affect homeostasis of the thyroid hormone signaling pathway. The development of the thyroid sodium/iodide symporter (NIS) assay is part of an effort lead by the Office of Research and Development to counteract this limitation by developing medium- and high-throughput screening assays that focus on molecular initiating events that could ultimately affect circulating thyroid hormone levels. To maintain sufficient concentrations of circulating thyroid hormones, the thyroid requires the active uptake of iodide as mediated by the NIS. Monovalent anions, such as the environmental contaminant perchlorate, have been well characterized as competitive inhibitors of NIS-mediated uptake of iodide, but limited information exists for more structurally diverse chemicals. The development of a screening approach to identify NIS inhibitors will enable the rapid prioritization of chemicals currently under the Agency's purview for further testing as potential thyroid disrupting activity.

Study Description: A novel cell line stably expressing human sodium iodide symporter (NIS), hNIS-HEK293T-EPA, was developed for use in a screening approach to identify chemicals that inhibit NIS-

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mediated radioactive iodide uptake (RAIU). For this RAIU assay, NIS-expressing cells were exposed to ^{125}I in the presence of serial dilutions of each test chemical ranging from 0.001 – 100mM. NIS-mediated ^{125}I uptake was then quantified to identify test chemicals that inhibit this action, indicated by decreased intracellular ^{125}I uptake relative to controls. Experiments were conducted to determine optimized assay conditions and to demonstrate assay performance using a set of reference chemicals containing known inhibitors of NIS-mediated iodide uptake and known inactive chemicals. This assay was used to screen chemicals in the ToxCast Phase 1_v2 chemical library for the potential to inhibit thyroid hormone synthesis by disrupting the NIS. A cell viability assay was subsequently conducted for each chemical used in the RAIU assay. A ranking system was developed based on the multi-concentration responses in the NIS assay and the confounding cytotoxicity for the 293 chemicals to inform the prioritization of the chemicals for secondary testing.

Research Results: Results from this study demonstrated that the NIS-mediated ^{125}I uptake assay is accurate, reproducible, and reliable for screening large libraries of chemicals. The ranking scores were assigned to chemicals which inhibited the NIS activity by more than 50% and allowed selection of chemicals with the potential to interfere with thyroid synthesis. Based on the ranking of the positives in the multi-concentration testing, approximately 21 of the 293 are being tested in follow-up secondary assays to confirm inhibitory activity.

Conclusion: The use of hNIS-HEK293T-EPA cells in the NIS-mediated iodide uptake and cell viability assays provide the U.S.EPA with a rapid approach for identifying chemicals that have the potential to disrupt a key molecular step essential for the synthesis of thyroid hormones. The screening and ranking of 293 chemicals in this study represents the first large scale effort to investigate NIS as a molecular target of environmental chemicals that covers a broad spectrum of structural and toxicological properties. These data can inform the prioritization of chemicals for secondary testing, and support the needs of the Endocrine Disruptor Screening Program for additional high-throughput in vitro assays to screen chemicals for interaction with more molecular targets that can disrupt normal thyroid hormone signaling. This assay and ranking approach can now be used for screening other larger chemical libraries such as the ToxCast Phase1_v2, Phase 2, and E1K libraries.¶

Contact: Tammy Stoker, Ph.D., [HYPERLINK "mailto:Stoker.Tammy@epa.gov"] (919) 541-2783 or Susan Laws, Ph.D., [HYPERLINK "mailto:Laws.Susan@epa.gov"] (919) 541-0173, Endocrine Toxicology Branch, Toxicity Assessment Division, NHEERL, ORD, U.S. EPA.

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 5/30/2017 1:44:10 PM
To: Wadlington, Christina [Wadlington.Christina@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: MCLG.Perchlorate Roll Out_5.15.17.docx
Attachments: MCLG.Perchlorate Roll Out_5.22_17_lc.docx

Hi Christina,
I'm okay with the changes and replied in the comment bubbles to questions.
Lisa

From: Wadlington, Christina
Sent: Tuesday, May 30, 2017 8:09 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: MCLG.Perchlorate Roll Out_5.15.17.docx

Morning!

I updated this document to address Jennifer's comment where I could.
Can you take a look at the rest and let me know if they are ok?

From: Mclain, Jennifer
Sent: Tuesday, May 30, 2017 8:00 AM
To: Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Fwd: MCLG.Perchlorate Roll Out_5.15.17.docx

Christina
A few comments on the perchlorate comm plan. Let me know if you want to discuss.
Thanks!
Jennifer

Perchlorate Peer Review
Communications Plan

PRE-PUBLICATION RELEASE DATE: Approximate Date, 2017

ACTION: The agency is undertaking an independent, external panel peer review and announces the release of several materials for public comment that relate to the development of a maximum contaminant level goal and a National Primary Drinking Water Regulation for perchlorate.

KEY MESSAGES

- Perchlorate – a chemical used in rocket propellants and other applications – can disrupt the normal function of the thyroid gland in both children and adults.
- EPA is currently determining the appropriate approach for deriving a Maximum Contaminant Level Goal (MCLG) for perchlorate.
- The agency initiated a peer review and is releasing the interim list of peer review candidates, draft charge questions as well as a draft MCLG approach report.
- The MCLG approach report provides information regarding how EPA intends to apply ~~BBDR~~ biological model outputs to the development of the perchlorate MCLG.
- The use of the ~~BBDR~~ biological model and draft approach to inform an MCLG is precedent-setting, therefore EPA is conducting a transparent and rigorous expert peer review process.
- After the peer review is complete, EPA will take the next appropriate steps.

ANTICIPATED REACTION

There is likely to be considerable interest and response to EPA's release of peer review materials and the peer review process itself. Over the past several years, stakeholders have provided extensive comments on publically reviewable perchlorate materials and notices, met with EPA senior officials, managers and staff and have wrote the Administrator numerous letters.

EPA was sued by NRDC for the Agency's failure to issue proposed and final regulatory actions for perchlorate in accordance with the timelines provided in SDWA. The court approved consent decree established a schedule for completing the peer review process (10/18/17) and signature of a proposed (10/31/18) and final rule (12/19/19).

Stakeholders and the press are aware that EPA has been working to implement SAB recommendations and develop a BBDR model and approach to inform development of an MCLG.

Stakeholders response will generally be critical of the ~~highly technical, underlying science to~~BBDR model ~~perchlorate in sensitive lifestages~~ and the ~~novel~~ application of the model output to inform derivation of a perchlorate MCLG.

- Stakeholder groups may state that EPA did not allow adequate time to conduct the scientific peer reviews.
- Industry groups (Perchlorate Study Group, American Chemistry Council); drinking water utilities, the U.S. Chamber of Commerce and the Department of Defense will likely be critical of the ~~underlying science~~model and EPA's application of the model.
- Environmental groups may state that EPA is altering the science to avoid regulation~~will likely be critical of the underlying science~~.
- Consumers, both those using public water systems and private wells, will be concerned about potential health risks from perchlorate.

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Perchlorate Peer Review
Communications Plan

DESK STATEMENT

Ensuring the safety of drinking water for all Americans is a top priority for EPA. The agency remains committed to completing the regulatory process for perchlorate in drinking water. The agency has initiated a peer review and is releasing peer review materials that inform decision making on perchlorate under the Safe Drinking Water Act. The materials include an interim list of peer review candidates, draft charge questions as well as a detailed report describing the approaches EPA developed for the biologically based dose-response model and information regarding how EPA intends to apply modeling to the development of the MCLG. After the peer review is complete, EPA will take the next appropriate steps on perchlorate under the Safe Drinking Water Act.

Background

On January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). This level was determined using a reference based dose response based on the recommendation of the National Research Council (NRC).

In 2011, EPA announced its decision (76 FR 7762) to regulate perchlorate under the Safe Drinking Water Act (SDWA). In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The MCLG is a non-enforceable goal defined under the SDWA as "the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." The MCLG is one of the considerations in developing the enforceable maximum contaminant level (MCL) for a regulated contaminant. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

As recommended by the SAB, the agency, with contributions from Food and Drug Administration scientists, developed a BBDR model to determine under what conditions of iodine nutrition and exposure to perchlorate, that infants and lactating mothers would experience hypothyroxinemia (changes in thyroid gland levels). EPA completed the peer review of the BBDR model. The report provided by the reviewers may be found on EPA's website at: https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water.

Legal Deadlines: On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

COMMUNICATIONS MATERIALS

Webpage (link will appear on https://www.epa.gov/dwstandardsregulations/perchlorate) will include:

- Link to public inspection FR notice
- Draft Charge Questions

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Perchlorate Peer Review
Communications Plan

- Interim List of Peer Reviewers
- Draft report on the application of the model to inform the development of a perchlorate MCLG

RELEASE SCHEDULE

-3 days

- OGWDW notification to Regional Contacts
- OPA notification to Regional PADS

-2 days

- OGWDW notification to federal partners (FDA, ATSDR, NIEHS)
- OPA calls to federal agencies' communications

Release Day (when publically available on FR site)

9:00 a.m	Begin head's up calls to stakeholder list below
10:00 a.m	Congressional heads up emails
12:00 p.m	Website goes live – Broader congressional notifications (emails with link to website).
1:00 p.m	Social media and stakeholder notification via email (Water Headlines listserv)

STAKEHOLDER NOTIFICATION

OGWDW:

- Michael Deane, Director, National Association of Water Companies
- Tracy Mehan, Government Affairs Director, American Water Works Association
- Mike Paque, Executive Director, Groundwater Protection Council
- Jim Taft, Executive Director, Association of State Drinking Water Administrators
- Lynn Thorp, National Campaigns Director, Clean Water Action
- Diane Van de Hei, Executive Director, Association of Metropolitan Water Agencies
- Sam Wade, Executive Director, National Rural Water Association
- Nathan Ohle, Rural Community Assistance Partnership

OGC:

- Eric Olson/Mae Wu, Natural Resources Defense Council

OLEM (OSRTI):

- Association of State and Territorial Solid Waste Management Officials

EXTERNAL QUESTIONS AND ANSWERS

CONSUMER QUESTIONS

Where is perchlorate found?

Perchlorate occurs naturally in arid states in the Southwest United States, in nitrate fertilizer deposits in Chile, and in potash ore in the United States and Canada. It also forms naturally in the atmosphere. Perchlorate is manufactured and used as an industrial chemical and can be found in rocket propellant, explosives, fireworks and road flares. It has been found in some public drinking water systems and in food.

Why is perchlorate in drinking water a health concern?

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Perchlorate Peer Review
Communications Plan

Perchlorate can disrupt the normal function of the thyroid gland in both children and adults. In adults, the thyroid plays an important role in metabolism, making and storing hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. In fetuses and infants, thyroid hormones are critical for normal growth and development of the central nervous system. Perchlorate can interfere with the human body's ability to absorb iodine into the thyroid gland which is a critical element in the production of thyroid hormones.

How does perchlorate get into my drinking water?
Perchlorate is dissolves easily, is relatively stable and is mobile in water. While it has often been detected in water supplies in close proximity to sites where solid rocket fuel is manufactured or used, there are also many locations in the United States lacking a clearly defined source.

Besides drinking water, how else can people be exposed to perchlorate?
People are exposed to perchlorate primarily through eating contaminated food or drinking water. The Food and Drug Administration (FDA) Total Diet Study combines nationwide sampling and analysis of hundreds of food items along with national surveys of food intake to develop comprehensive dietary exposure estimates for a variety of demographic groups in the U.S. In the 2008-2012 survey the FDA found detectable levels of perchlorate in 97 percent of the foods sampled. The complete set of FDA perchlorate data can be found here:
[HYPERLINK "https://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077615.htm"]

Have public drinking water systems been sampled for perchlorate?
Customers served by a public water system can contact their local water supplier and ask if they test for perchlorate. If so, they are encouraged to obtain a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state standards or guidelines.

The most recent Consumer Confidence Report can be obtained from your drinking water utility by visiting their website or contacting them for a copy. Some public water systems upload their Consumer Confidence Report to EPA's website at: [HYPERLINK "http://www.epa.gov/ccr" \h].

Also, if your public water system participated in collecting monitoring data for UCMR 1, you can find information about your system at: [HYPERLINK "https://www.epa.gov/dwucmr/first-unregulated-contaminant-monitoring-rule"].

I live in a community with elevated perchlorate levels. Who do I call to get more information about what my utility is doing to address the elevated levels?
Contact your local water supplier to find out more about perchlorate in your drinking water. If you don't know who your local water supplier is, the information should be included in your latest water bill.

I get my tap water from a private well. How can I find out if perchlorate are in my water?
If you are concerned about the possibility of perchlorate in your drinking water and you are served by a private well, EPA recommends testing your drinking water. Approved laboratories can analyze a sample of your water to determine whether perchlorates are present and at what concentrations. Your local

water or health department or drinking water system should know if there is such a program in your area. In addition, EPA recommends that residents reach out to their local public health department or state who may be able to help provide support for testing or to seek such support from a responsible party. If no program has been established or support is not available in your area, you can pay to have independent testing done at a qualified testing lab (typical cost is several hundred dollars per sample).

More information about private wells can be found here: [HYPERLINK "http://www.epa.gov/privatewells" \h].

Can a person drink tap water containing perchlorate at or below the level of the health advisory every day of their life and not expect adverse health effects from these chemicals?
Yes, the EPA health advisory level offers a margin of protection for all Americans from adverse health effects for a lifetime of exposure to perchlorate in drinking water at 15ppb.

Can perchlorate be boiled out of my water?
No, perchlorate cannot be removed by heating or boiling water.

How does a utility reduce/remove perchlorate?
A number of options are available to drinking water systems to lower concentrations of perchlorate in the drinking water supply. In some cases, drinking water systems may be able to reduce concentrations of perchlorate by closing contaminated wells or changing rates of blending of water sources. Perchlorate can be removed using a number of advanced treatment techniques. Each technique has advantages and disadvantages depending on the level of perchlorate present in the source water, removal goals, other water quality parameters, competing treatment objectives, and treatment waste disposal options. Regenerable and single-pass ion exchange, reverse osmosis, and fixed- and fluidized-bed biological treatment can all remove perchlorate from drinking water sources.

These treatment systems are used by some public water systems today, but should be carefully designed and maintained to ensure that they are effective for treating perchlorate.

Can I buy a home treatment device to remove perchlorate?
If you are concerned about perchlorate in your drinking water, you may consider purchasing a home treatment device such as a filter. However, in order to make a well-informed and cost-effective decision, consider checking with your water system or consumer confidence report to learn about the amount of total perchlorate in your water and identifying a device that has been independently certified to remove perchlorate.

[HYPERLINK "http://www.nsf.org/consumer-resources/what-is-nsf-certification/water-filters-treatment-certification/contaminant-reduction-claims-guide" \t "_blank"], the [HYPERLINK "https://www.wqa.org/" \t "_blank"], [HYPERLINK "http://ul.com/" \t "_blank"] and [HYPERLINK "http://www.csagroup.org/global/en/services/testing-and-certification" \t "_blank"] all certify home treatment products for removal of contaminants. The relevant perchlorate removal standard is [HYPERLINK "http://www.nsf.org/consumer-resources/health-and-safety-tips/water-quality-treatment-tips/standards-for-water-treatment-systems" \t "_blank"]. If you choose to use a home treatment device, it is very important to follow the manufacturer's operation and maintenance instructions carefully in order to make sure the device works properly.

Commented [CW1]: TAB, is this still accurate?

Commented [CL2R1]: yes

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Perchlorate Peer Review
Communications Plan

Does perchlorate have a health advisory level?
Yes, on January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). More information on the Interim Drinking Water Health Advisory for perchlorate can be found here: [HYPERLINK "http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.txt"]

Has a safe level of exposure for perchlorate been established?
On February 11, 2011, EPA determined that perchlorate meets the Safe Drinking Water Act criteria for regulation as a contaminant. The Agency found that perchlorate may have an adverse effect on the health of persons and is known to occur in public drinking water systems with a frequency and at levels that present a public health concern. Since that time, EPA has been reviewing the best available scientific data on a range of issues related to perchlorate in drinking water including its occurrence, treatment technologies, analytical methods and the costs and benefits of potential standards.

There also have been state actions on perchlorate standards, guidelines, and advisories. In 2006, Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L, and in 2007, California promulgated a standard of 6 µg/L. Twelve other states have established non-enforceable guidance levels, action or advisory levels. Depending on the state, a particular level may require a public water system to notify the public, serve as a screening tool for further action, or guide clean-up actions.

Customers that are served by a public water system can contact their local water supplier and ask for information on perchlorate in their drinking water, and are encouraged to request a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state and EPA drinking water standards.

PEER REVIEW QUESTIONS

Why is EPA conducting a peer review?
EPA will ask peer reviewers to comment on products that the agency will use to inform decision making on perchlorate under the Safe Drinking Water Act

EPA believes that peer review is an important component of the scientific process. The critical feedback, suggestions, and new ideas provided by the peer reviewers stimulate creative thought, strengthen the interpretation of the reviewed material, and confer credibility on the product. The peer review objective is to provide advice to EPA on steps that will yield a highly credible scientific product that is supported by the scientific community.

What products will be reviewed?
Peer reviewers will be asked to comment on the draft report entitled "Peer Review Draft: Proposed Approach to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water." EPA is seeking public comments on this report and also on the peer review charge and the interim list of expert peer review panel candidates.

Where can I find the review products?
All documents in the docket are listed on the [HYPERLINK "http://www.regulations.gov"] website under Docket ID Numbers EPA-HQ-OW-2016-0438 and EPA-HQ-OW-2016-0439.

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Perchlorate Peer Review
Communications Plan

Can I provide comments on the review products?
Yes. The public will have an opportunity to review and comment on the draft charge questions, the interim list of peer reviewers and the draft report describing application of the model to inform development of a perchlorate MCLG.

Additionally, we intend to allow for people to make brief statements during the meeting, and any Safe Drinking Water Act regulation on perchlorate will be subject to public notice and comment.

How long is the comment period?
EPA announced that its seeking public comments on two separate sets of materials. The first set is the interim list of peer review candidates and the draft charge questions. People should send their comments to Versar, Inc. no later than 21 days after publication in the Federal Register.

A companion notice, also published on the same date, requests comments on the draft report on application of the model to inform derivation of a perchlorate MCLG. People should send their comments to the docket no later than 45 days after publication in the Federal Register.

Will the review panelists see my comments or just EPA?
EPA will provide panelists a summary of the public comments submitted on the draft products.

When and where will EPA hold the meeting?
The meeting is projected to occur during in the fall of 2017 (exact date to be determined). EPA will announce the meeting in the Federal Register at least 30 days in advance to provide the meeting date, location and registration information. EPA anticipates holding the two-day meeting in the Washington, DC metro area.

What will EPA do with the public comments and panel recommendations?
A peer review summary report will be developed that contains the final comments and recommendations from the peer reviewers. EPA will make the final peer review report available to the public.

EPA will consider any public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the documents.

How will the contractor select the reviewers?
The contractor considered and screened all candidates against the selection criteria described in the March 1, 2016, and June 3, 2016, Federal Register notices (81 FR 10617 and 81 FR 35760, respectively) which included being free of any conflict of interest and being available to participate in-person in the peer review meeting.

Following the screening process, the list was narrowed to 12 candidates. EPA is now soliciting comments on the interim list of 12 candidates. Once the public comments on the interim list of candidates have been reviewed and considered, and the Science Integrity Official has been consulted, the final list of peer reviewers will be selected.

What happens next?

Perchlorate Peer Review
Communications Plan

Once the public comments on the interim list of candidates have been reviewed and considered, the final list of peer reviewers will be selected.

What happens after the peer reviewers are selected?
Following the selection process, the peer reviewers will be tasked with evaluating and providing written comments on the draft products. Additionally, peer reviewers will be provided a summary of public comments and given access to public comments submitted during the draft document's public comment period.

When will EPA establish a national drinking water standard for perchlorate?
EPA will ~~to~~ consider ~~public comments and~~ peer reviewer comments and public comments submitted in accordance with the Federal Register notice when finalizing the ~~peer review products~~materials that inform decision making on perchlorate under the SDWA. After the peer review is complete, EPA will take the next appropriate steps on perchlorate under the SDWA.

INTERNAL QUESTIONS AND ANSWERS

Why is it taking so long for us to regulate perchlorate?
In 2011, EPA announced its decision to regulate perchlorate under the Safe Drinking Water Act (SDWA).

In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

The agency, with contributions from Food and Drug Administration scientists, spent over two years to develop the model that accounts for population differences in iodide exposure and predicts changes in thyroid hormone levels that result from exposure to perchlorate.

Commented [MJ3]: Three?

Commented [CL4R3]: Two, unless you want to count the time revising the BBDR model post peer review

What is the status of the NRDC complaint? (CLEAR WITH OGC)
On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

Will the peer review products present alternative MCLGs?
No, the documents will not present alternative MCLGs, however some experts can be expected to predict the MCLGs that would result from using the methodologies that are described in the documents.

Will the methodologies that will be presented to the peer reviewers result in MCLGs that are in the range of MCLs set by California (6 µg/L) and Massachusetts (2 µg/L)?

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Yes. Additionally, 12 states have guidance levels: AZ, FL, IL, KS, MD, NV, NJ, NM, NY, OR, TX, VT. The drinking water levels range from 1 to 18 µg/L. These levels may trigger public notice, serve as a screening tool for further action or guide cleanup action.

Commented [MJ5]: Is this correct?

Commented [CL6R5]: Suggest deleting this questions… Modified BBDR model results and potential doses are being incorporated into the report now. Previous iterations had concentrations higher the 2 ppb or 6 ppb

What is our evaluation of perchlorate occurrence data?

The UCMR 1 perchlorate dataset is the best available nationally representative data on perchlorate occurrence in public water systems. Analytical detections of perchlorate at or above the minimum reporting level (4 µg/L) were identified in about 4% (155 of 3,865) of these systems. EPA estimates that between 5.1 million to 16.6 million people served by the sampled systems could be exposed to perchlorate in drinking water. While perchlorate analytical detections are fairly numerous and widespread geographically, the UCMR 1 findings indicate that perchlorate occurs at relatively low levels: about 85% of analytical perchlorate detections are less than 13 µg/L and 42% are less than 6 µg/L.

However, commenters have pointed out limitations of UCMR 1 for estimating current occurrence. The minimum reporting level is 4 µg/L. Since UCMR 1 data has been collected, 2 states have enacted perchlorate standards (CA & MA) and remediation activities or new sources of perchlorate may have impacted concentration levels in public water systems.

Are there any cross-office implications of promulgating a drinking water regulation?
Yes, promulgating a drinking water regulation for perchlorate would become the applicable or relevant and appropriate requirement (ARAR) and would replace the current preliminary remediation goal (PRG) for CERCLA sites (current PRG is based on the Interim Drinking Water Health Advisory level of 15 µg/L).

Is there an Environmental Justice/Equity component for the affected communities?
Each community faces unique challenges when addressing concerns related to environmental issues. Perchlorates in drinking water are related to localized sources of contamination often near where these produced have been manufactured or produced. Currently, if water sampling results confirm that drinking water contains perchlorate at individual or combined concentrations greater than 15 parts per billion, water systems should undertake additional sampling to assess the level, scope and localized source of contamination to inform next steps.

How will the RfD, or the interim health advisory, be used to inform the MCLG?
Based on SAB recommendations EPA does not intend to use the perchlorate RfD to inform derivation of an MCLG. The SAB stated that it, ". . . recognizes that this is a novel approach as compared to previous MCLG derivations that use the RfD and exposure factors. However, PBPK/PDIUI modeling provides a more rigorous tool to integrate the totality of information available on perchlorate, and this approach may better address different life stage susceptibilities to perchlorate than the default MCLG approach."

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Message

From: Messier, Dawn [Messier.Dawn@epa.gov]
Sent: 3/22/2017 7:04:41 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: RE: Perchlorate peer review report
Attachments: 1 pager perchlorate in drinking waterdmm.doc

A few comments. Thanks! Dawn

Dawn Messier
U.S.E.P.A.
Office of General Counsel
Water Law Office
202-564-5517

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 1:56 PM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: RE: Perchlorate peer review report

Yvonne; Please see the draft note to Mike about perchlorate peer review. Also please find attached a draft one pager for the A.0. describing our activities. Please note the attached is still under review by OGC but I am sending to you and copying Dawn so that she can convey and comments/concerns to all once she has had a chance to review.

Mike:
Please find attached, a one page summary of our activities on perchlorate. The attached provides background information, identifies key issues and a timeline for moving forward. The attached highlights the recently completed peer review of the biologically based dose response (BBDR) model for perchlorate and the planned peer review of methodologies to develop alternative MCLGs using the BBDR model.

Please note that we recently received the final peer review report for the BBDR model. We plan to post this peer review document to our docket so that the public will be able to view the recommendations we have received for how to improve the BBDR model. The peer reviewers identified a number of areas for improvement or modification of the existing model for predicting thyroid hormone level changes caused by perchlorate exposure. The peer reviewers recommended that the Agency develop a plan for further actions in order to maximize the benefit of any model revisions that are undertaken and to make decisions about priorities, timelines, and resources. Peer reviewers noted that models can always be improved, but the goal is to have a model that is fit for the intended purpose. The peer reviewers noted that the lack of a clear definition of that purpose for this model (i.e., how the model outputs would be used in developing the desired drinking water regulations) contributed to the difficulty they had in assessing whether the model was sufficiently good to apply.

We are working with our colleagues in ORD and FDA to implement many of the recommendations the peer reviewers made to the BBDR model. We believe that the purpose of the BBDR model will be more evident with the preparation of the MCLG Report that will describe alternative approaches for applying the BBDR model to develop potential perchlorate MCLGs. We hope to brief the Administrator's office on the perchlorate peer review process in April and intend to cover the recommendations from the first peer review and the draft MCLG report in April.

Please let us know if there is any more information you would like us to prepare in order inform the Administrator's office of these important activities.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 1:28 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Perchlorate peer review report

Eric,

Ann and I were on the same page. She thought an email note from Peter to Mike would suffice , including something on the findings and recommendations contained in the report.
I was just sending a heads up to Christina about the Desk Statement and holding it till we get an ok.

Can you or Lisa provide a draft of the email for Peter?

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 1:26 PM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate peer review report

I spoke with Jennifer about this and one idea we have is to mention posting the peer review report in the note that Ann/Mike will send to the A.O.
The draft one pager for perchlorate is under review by OGC since it references the Consent Decree.

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 11:56 AM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate peer review report

I don't recall specifically mentioning placing the peer review report in the docket to Mike. We of course have spoken about conducting the peer review, we just did not get into the specifics of putting the report into the docket.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 11:48 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Perchlorate peer review report

> Eric,
> Jennifer and I do not recall teeing up (at the bi-weekly or LCR meetings) the Perchlorate peer review report and placing it in the docket to Mike. Do you or Lisa remember doing so? Anything Please advise. I don't want to hold anything up on the comms side, but I also know Ann is going to ask if we did.

DESK STATEMENT

To ensure the safety of drinking water for all Americans, EPA is continuing the regulatory process for perchlorate in drinking water. In response to recommendations from our Science Advisory Board, the agency is developing two new analyses to inform selection of a health based goal (the Maximum Contaminant Level Goal or MCLG) for the regulation. The first new analysis is the development of a biologically based dose response (BBDR) model and the second analysis is the development of methodologies to derive a MCLG for the regulation using the BBDR model. The agency held a peer review of the first of two new analyses to ensure the agency's perchlorate regulatory decision-making is based on the best available science. EPA has received the peer review report, is reviewing the recommendations and will be taking actions to improve the BBDR model as appropriate. EPA plans to conduct a second peer review of the second analyses describes methodologies for deriving a MCLG for using the BBDR model. To find a copy of the report please visit:
https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN 2040-AF28, significant

Purpose: To improve the health protection to drinking water consumers from perchlorate.

Background: On February 11, 2011, EPA announced its decision to regulate perchlorate based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant. SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013) and finalize the regulations 18 months after proposal (can extend up to 9 months).

Stakeholder Involvement: EPA consulted with the National Drinking Water Advisory Council in 2012 on potential requirements of the perchlorate regulation. EPA has also met or corresponded with industry groups including the Perchlorate Study Group, American Chemistry Council, the American Water Works Association and the U.S. Chamber of Commerce. EPA was sued by the Natural Resources Defense Council in 2016 for the Agency's failure to issue proposed and final regulations for perchlorate in accordance with SDWA timelines.

Key Issues/Internal Review: The key issue for perchlorate is establishing the Maximum Contaminant Level Goal (MCLG[1]) which is defined in SDWA as the "level at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety." In early 2012, ~~EPA~~ the Agency sought recommendations from ~~the~~ EPA's Science Advisory Board on how to derive a MCLG for perchlorate in accordance with SDWA. The SAB recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling." In response to SAB recommendations, FDA and EPA scientists worked to develop models to relate perchlorate exposure to biological effects to infants ~~,~~ and other life stages. EPA completed an expert peer review of the models, and we are preparing for a second expert peer review of methodologies to apply the model to identify potential MCLGs for perchlorate. Once peer review of these analyses are completed, OW will brief the Administrator and seek input on at what level the MCLG should be set and whether the Agency should proceed with a perchlorate rulemaking (EPA could withdraw the determination to regulate by publishing a preliminary determination not to regulate for public comment and

Commented [DMM1]: Just in case the reader is unfamiliar with the SAB

Commented [DMM2]: ??How about "EPA reads the SDWA to allow the Agency to withdraw the determination to regulate through a new round of notice and comment rulemaking."

Legal Deadlines: EPA is under a consent decree with enforceable dates of October 31, 2018 for signature of a proposed MCLG and NPDWR ~~action~~ and a signature date of December 19, 2019 for the finale ~~action~~MCLG and NPDWR for perchlorate.

Timing: In order to complete necessary analyses for development of a proposed rule, including the Heath Risk Reduction Cost Analysis required by SDWA, we will need to

[1] Maximum Contaminant Level Goal (MCLG) is a non-enforceable public health goal. The enforceable standard, the Maximum Contaminant Level (MCL) ~~The MCL~~ is set as close to the MCLG as feasible using best available treatment technology and taking cost into consideration.

initiate expert peer review of the approaches to derive an MCLG in mid May and complete the review in October 2017. We would like to brief the A.O. about peer review in April.

Message

From: Wadlington, Christina [Wadlington.Christina@epa.gov]
Sent: 5/30/2017 12:09:04 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: RE: MCLG.Perchlorate Roll Out_5.15.17.docx
Attachments: MCLG.Perchlorate Roll Out_5.22.docx

Morning!

I updated this document to address Jennifer's comment where I could.
Can you take a look at the rest and let me know if they are ok?

From: Mclain, Jennifer
Sent: Tuesday, May 30, 2017 8:00 AM
To: Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Fwd: MCLG.Perchlorate Roll Out_5.15.17.docx

Christina
A few comments on the perchlorate comm plan. Let me know if you want to discuss.
Thanks!
Jennifer

Perchlorate Peer Review
Communications Plan

PRE-PUBLICATION RELEASE DATE: Approximate Date, 2017

ACTION: The agency is undertaking an independent, external panel peer review and announces the release of several materials for public comment that relate to the development of a maximum contaminant level goal and a National Primary Drinking Water Regulation for perchlorate.

KEY MESSAGES

- Perchlorate – a chemical used in rocket propellants and other applications – can disrupt the normal function of the thyroid gland in both children and adults.
- EPA is currently determining the appropriate approach for deriving a Maximum Contaminant Level Goal (MCLG) for perchlorate.
- The agency initiated a peer review and is releasing the interim list of peer review candidates, draft charge questions as well as a draft MCLG approach report.
- The MCLG approach report provides information regarding how EPA intends to apply ~~BBDR~~ biological model outputs to the development of the perchlorate MCLG.
- The use of the ~~BBDR~~ biological model and draft approach to inform an MCLG is precedent-setting, therefore EPA is conducting a transparent and rigorous expert peer review process.
- After the peer review is complete, EPA will take the next appropriate steps.

ANTICIPATED REACTION

There is likely to be considerable interest and response to EPA's release of peer review materials and the peer review process itself. Over the past several years, stakeholders have provided extensive comments on publically reviewable perchlorate materials and notices, met with EPA senior officials, managers and staff and have wrote the Administrator numerous letters.

EPA was sued by NRDC for the Agency's failure to issue proposed and final regulatory actions for perchlorate in accordance with the timelines provided in SDWA. The court approved consent decree established a schedule for completing the peer review process (10/18/17) and signature of a proposed (10/31/18) and final rule (12/19/19).

Stakeholders and the press are aware that EPA has been working to implement SAB recommendations and develop a BBDR model and approach to inform development of an MCLG.

Stakeholders response will generally be critical of the ~~highly technical, underlying science to~~BBDR model ~~perchlorate in sensitive lifestages~~ and the ~~novel~~ application of the model output to inform derivation of a perchlorate MCLG.

- Stakeholder groups may state that EPA did not allow adequate time to conduct the scientific peer reviews.
- Industry groups (Perchlorate Study Group, American Chemistry Council); drinking water utilities, the U.S. Chamber of Commerce and the Department of Defense will likely be critical of the ~~underlying science~~model and EPA's application of the model.
- Environmental groups may state that EPA is altering the science to avoid regulation~~will likely be critical of the underlying science~~.
- Consumers, both those using public water systems and private wells, will be concerned about potential health risks from perchlorate.

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Perchlorate Peer Review
Communications Plan

DESK STATEMENT

Ensuring the safety of drinking water for all Americans is a top priority for EPA. The agency remains committed to completing the regulatory process for perchlorate in drinking water. The agency has initiated a peer review and is releasing peer review materials that inform decision making on perchlorate under the Safe Drinking Water Act. The materials include an interim list of peer review candidates, draft charge questions as well as a detailed report describing the approaches EPA developed for the biologically based dose-response model and information regarding how EPA intends to apply modeling to the development of the MCLG. After the peer review is complete, EPA will take the next appropriate steps on perchlorate under the Safe Drinking Water Act.

Background

On January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). This level was determined using a reference based dose response based on the recommendation of the National Research Council (NRC).

In 2011, EPA announced its decision (76 FR 7762) to regulate perchlorate under the Safe Drinking Water Act (SDWA). In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The MCLG is a non-enforceable goal defined under the SDWA as "the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." The MCLG is one of the considerations in developing the enforceable maximum contaminant level (MCL) for a regulated contaminant. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

As recommended by the SAB, the agency, with contributions from Food and Drug Administration scientists, developed a BBDR model to determine under what conditions of iodine nutrition and exposure to perchlorate, that infants and lactating mothers would experience hypothyroxinemia (changes in thyroid gland levels). EPA completed the peer review of the BBDR model. The report provided by the reviewers may be found on EPA's website at: https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water.

Legal Deadlines: On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

COMMUNICATIONS MATERIALS

Webpage (link will appear on https://www.epa.gov/dwstandardsregulations/perchlorate) will include:

- Link to public inspection FR notice
- Draft Charge Questions

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Perchlorate Peer Review
Communications Plan

- Interim List of Peer Reviewers
- Draft report on the application of the model to inform the development of a perchlorate MCLG

RELEASE SCHEDULE

-3 days

- OGWDW notification to Regional Contacts
- OPA notification to Regional PADS

-2 days

- OGWDW notification to federal partners (FDA, ATSDR, NIEHS)
- OPA calls to federal agencies' communications

Release Day (when publically available on FR site)

9:00 a.m	Begin head's up calls to stakeholder list below
10:00 a.m	Congressional heads up emails
12:00 p.m	Website goes live – Broader congressional notifications (emails with link to website).
1:00 p.m	Social media and stakeholder notification via email (Water Headlines listserv)

STAKEHOLDER NOTIFICATION

OGWDW:

- Michael Deane, Director, National Association of Water Companies
- Tracy Mehan, Government Affairs Director, American Water Works Association
- Mike Paque, Executive Director, Groundwater Protection Council
- Jim Taft, Executive Director, Association of State Drinking Water Administrators
- Lynn Thorp, National Campaigns Director, Clean Water Action
- Diane Van de Hei, Executive Director, Association of Metropolitan Water Agencies
- Sam Wade, Executive Director, National Rural Water Association
- Nathan Ohle, Rural Community Assistance Partnership

OGC:

- Eric Olson/Mae Wu, Natural Resources Defense Council

OLEM (OSRTI):

- Association of State and Territorial Solid Waste Management Officials

EXTERNAL QUESTIONS AND ANSWERS

CONSUMER QUESTIONS

Where is perchlorate found?

Perchlorate occurs naturally in arid states in the Southwest United States, in nitrate fertilizer deposits in Chile, and in potash ore in the United States and Canada. It also forms naturally in the atmosphere. Perchlorate is manufactured and used as an industrial chemical and can be found in rocket propellant, explosives, fireworks and road flares. It has been found in some public drinking water systems and in food.

Why is perchlorate in drinking water a health concern?

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Perchlorate Peer Review
Communications Plan

Perchlorate can disrupt the normal function of the thyroid gland in both children and adults. In adults, the thyroid plays an important role in metabolism, making and storing hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. In fetuses and infants, thyroid hormones are critical for normal growth and development of the central nervous system. Perchlorate can interfere with the human body's ability to absorb iodine into the thyroid gland which is a critical element in the production of thyroid hormones.

How does perchlorate get into my drinking water?
Perchlorate is dissolves easily, is relatively stable and is mobile in water. While it has often been detected in water supplies in close proximity to sites where solid rocket fuel is manufactured or used, there are also many locations in the United States lacking a clearly defined source.

Besides drinking water, how else can people be exposed to perchlorate?
People are exposed to perchlorate primarily through eating contaminated food or drinking water. The Food and Drug Administration (FDA) Total Diet Study combines nationwide sampling and analysis of hundreds of food items along with national surveys of food intake to develop comprehensive dietary exposure estimates for a variety of demographic groups in the U.S. In the 2008-2012 survey the FDA found detectable levels of perchlorate in 97 percent of the foods sampled. The complete set of FDA perchlorate data can be found here:
[HYPERLINK "https://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077615.htm"]

Have public drinking water systems been sampled for perchlorate?
Customers served by a public water system can contact their local water supplier and ask if they test for perchlorate. If so, they are encouraged to obtain a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state standards or guidelines.

The most recent Consumer Confidence Report can be obtained from your drinking water utility by visiting their website or contacting them for a copy. Some public water systems upload their Consumer Confidence Report to EPA's website at: [HYPERLINK "http://www.epa.gov/ccr" \h].

Also, if your public water system participated in collecting monitoring data for UCMR 1, you can find information about your system at: [HYPERLINK "https://www.epa.gov/dwucmr/first-unregulated-contaminant-monitoring-rule"].

I live in a community with elevated perchlorate levels. Who do I call to get more information about what my utility is doing to address the elevated levels?
Contact your local water supplier to find out more about perchlorate in your drinking water. If you don't know who your local water supplier is, the information should be included in your latest water bill.

I get my tap water from a private well. How can I find out if perchlorate are in my water?
If you are concerned about the possibility of perchlorate in your drinking water and you are served by a private well, EPA recommends testing your drinking water. Approved laboratories can analyze a sample of your water to determine whether perchlorates are present and at what concentrations. Your local

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water or health department or drinking water system should know if there is such a program in your area. In addition, EPA recommends that residents reach out to their local public health department or state who may be able to help provide support for testing or to seek such support from a responsible party. If no program has been established or support is not available in your area, you can pay to have independent testing done at a qualified testing lab (typical cost is several hundred dollars per sample).

More information about private wells can be found here: [HYPERLINK "http://www.epa.gov/privatewells" \h].

Can a person drink tap water containing perchlorate at or below the level of the health advisory every day of their life and not expect adverse health effects from these chemicals?
Yes, the EPA health advisory level offers a margin of protection for all Americans from adverse health effects for a lifetime of exposure to perchlorate in drinking water at 15ppb.

Can perchlorate be boiled out of my water?
No, perchlorate cannot be removed by heating or boiling water.

How does a utility reduce/remove perchlorate?
A number of options are available to drinking water systems to lower concentrations of perchlorate in the drinking water supply. In some cases, drinking water systems may be able to reduce concentrations of perchlorate by closing contaminated wells or changing rates of blending of water sources. Perchlorate can be removed using a number of advanced treatment techniques. Each technique has advantages and disadvantages depending on the level of perchlorate present in the source water, removal goals, other water quality parameters, competing treatment objectives, and treatment waste disposal options. Regenerable and single-pass ion exchange, reverse osmosis, and fixed- and fluidized-bed biological treatment can all remove perchlorate from drinking water sources.

These treatment systems are used by some public water systems today, but should be carefully designed and maintained to ensure that they are effective for treating perchlorate.

Can I buy a home treatment device to remove perchlorate?
If you are concerned about perchlorate in your drinking water, you may consider purchasing a home treatment device such as a filter. However, in order to make a well-informed and cost-effective decision, consider checking with your water system or consumer confidence report to learn about the amount of total perchlorate in your water and identifying a device that has been independently certified to remove perchlorate.

[HYPERLINK "http://www.nsf.org/consumer-resources/what-is-nsf-certification/water-filters-treatment-certification/contaminant-reduction-claims-guide" \t "_blank"], the [HYPERLINK "https://www.wqa.org/" \t "_blank"], [HYPERLINK "http://ul.com/" \t "_blank"] and [HYPERLINK "http://www.csagroup.org/global/en/services/testing-and-certification" \t "_blank"] all certify home treatment products for removal of contaminants. The relevant perchlorate removal standard is [HYPERLINK "http://www.nsf.org/consumer-resources/health-and-safety-tips/water-quality-treatment-tips/standards-for-water-treatment-systems" \t "_blank"]. If you choose to use a home treatment device, it is very important to follow the manufacturer's operation and maintenance instructions carefully in order to make sure the device works properly.

Commented [CW1]: TAB, is this still accurate?

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Perchlorate Peer Review
Communications Plan

Does perchlorate have a health advisory level?
Yes, on January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb).More information on the Interim Drinking Water Health Advisory for perchlorate can be found here: [HYPERLINK "http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.txt"]

Has a safe level of exposure for perchlorate been established?
On February 11, 2011, EPA determined that perchlorate meets the Safe Drinking Water Act criteria for regulation as a contaminant. The Agency found that perchlorate may have an adverse effect on the health of persons and is known to occur in public drinking water systems with a frequency and at levels that present a public health concern. Since that time, EPA has been reviewing the best available scientific data on a range of issues related to perchlorate in drinking water including its occurrence, treatment technologies, analytical methods and the costs and benefits of potential standards.

There also have been state actions on perchlorate standards, guidelines, and advisories. In 2006, Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L, and in 2007, California promulgated a standard of 6 µg/L. Twelve other states have established non-enforceable guidance levels, action or advisory levels. Depending on the state, a particular level may require a public water system to notify the public, serve as a screening tool for further action, or guide clean-up actions.

Customers that are served by a public water system can contact their local water supplier and ask for information on perchlorate in their drinking water, and are encouraged to request a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state and EPA drinking water standards.

PEER REVIEW QUESTIONS

Why is EPA conducting a peer review?
EPA will ask peer reviewers to comment on products that the agency will use to inform decision making on perchlorate under the Safe Drinking Water Act

EPA believes that peer review is an important component of the scientific process. The critical feedback, suggestions, and new ideas provided by the peer reviewers stimulate creative thought, strengthen the interpretation of the reviewed material, and confer credibility on the product. The peer review objective is to provide advice to EPA on steps that will yield a highly credible scientific product that is supported by the scientific community.

What products will be reviewed?
Peer reviewers will be asked to comment on the draft report entitled "Peer Review Draft: Proposed Approach to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water." EPA is seeking public comments on this report and also on the peer review charge and the interim list of expert peer review panel candidates.

Where can I find the review products?
All documents in the docket are listed on the [HYPERLINK "http://www.regulations.gov"] website under Docket ID Numbers EPA-HQ-OW-2016-0438 and EPA-HQ-OW-2016-0439.

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Perchlorate Peer Review
Communications Plan

Can I provide comments on the review products?
Yes. The public will have an opportunity to review and comment on the draft charge questions, the interim list of peer reviewers and the draft report describing application of the model to inform development of a perchlorate MCLG.

Additionally, we intend to allow for people to make brief statements during the meeting, and any Safe Drinking Water Act regulation on perchlorate will be subject to public notice and comment.

How long is the comment period?
EPA announced that its seeking public comments on two separate sets of materials. The first set is the interim list of peer review candidates and the draft charge questions. People should send their comments to Versar, Inc. no later than 21 days after publication in the Federal Register.

A companion notice, also published on the same date, requests comments on the draft report on application of the model to inform derivation of a perchlorate MCLG. People should send their comments to the docket no later than 45 days after publication in the Federal Register.

Will the review panelists see my comments or just EPA?
EPA will provide panelists a summary of the public comments submitted on the draft products.

When and where will EPA hold the meeting?
The meeting is projected to occur during in the fall of 2017 (exact date to be determined). EPA will announce the meeting in the Federal Register at least 30 days in advance to provide the meeting date, location and registration information. EPA anticipates holding the two-day meeting in the Washington, DC metro area.

What will EPA do with the public comments and panel recommendations?
A peer review summary report will be developed that contains the final comments and recommendations from the peer reviewers. EPA will make the final peer review report available to the public.

EPA will consider any public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the documents.

How will the contractor select the reviewers?
The contractor considered and screened all candidates against the selection criteria described in the March 1, 2016, and June 3, 2016, Federal Register notices (81 FR 10617 and 81 FR 35760, respectively) which included being free of any conflict of interest and being available to participate in-person in the peer review meeting.

Following the screening process, the list was narrowed to 12 candidates. EPA is now soliciting comments on the interim list of 12 candidates. Once the public comments on the interim list of candidates have been reviewed and considered, and the Science Integrity Official has been consulted, the final list of peer reviewers will be selected.

What happens next?

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Perchlorate Peer Review
Communications Plan

Once the public comments on the interim list of candidates have been reviewed and considered, the final list of peer reviewers will be selected.

What happens after the peer reviewers are selected?
Following the selection process, the peer reviewers will be tasked with evaluating and providing written comments on the draft products. Additionally, peer reviewers will be provided a summary of public comments and given access to public comments submitted during the draft document's public comment period.

When will EPA establish a national drinking water standard for perchlorate?
EPA will to consider public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the ~~peer review products~~materials that inform decision making on perchlorate under the SDWA. After the peer review is complete, EPA will take the next appropriate steps on perchlorate under the SDWA.

INTERNAL QUESTIONS AND ANSWERS

Why is it taking so long for us to regulate perchlorate?
In 2011, EPA announced its decision to regulate perchlorate under the Safe Drinking Water Act (SDWA).

In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

The agency, with contributions from Food and Drug Administration scientists, spent over two years to develop the model that accounts for population differences in iodide exposure and predicts changes in thyroid hormone levels that result from exposure to perchlorate.

Commented [MJ2]: Three?

What is the status of the NRDC complaint? (CLEAR WITH OGC)
On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

Will the peer review products present alternative MCLGs?
No, the documents will not present alternative MCLGs, however some experts can be expected to predict the MCLGs that would result from using the methodologies that are described in the documents.

Will the methodologies that will be presented to the peer reviewers result in MCLGs that are in the range of MCLs set by California (6 µg/L) and Massachusetts (2 µg/L)?

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Yes. Additionally, 12 states have guidance levels: AZ, FL, IL, KS, MD, NV, NJ, NM, NY, OR, TX, VT. The drinking water levels range from 1 to 18 µg/L. These levels may trigger public notice, serve as a screening tool for further action or guide cleanup action.

Commented [MJ3]: Is this correct?

What is our evaluation of perchlorate occurrence data?

The UCMR 1 perchlorate dataset is the best available nationally representative data on perchlorate occurrence in public water systems. Analytical detections of perchlorate at or above the minimum reporting level (4 µg/L) were identified in about 4% (155 of 3,865) of these systems. EPA estimates that between 5.1 million to 16.6 million people served by the sampled systems could be exposed to perchlorate in drinking water. While perchlorate analytical detections are fairly numerous and widespread geographically, the UCMR 1 findings indicate that perchlorate occurs at relatively low levels: about 85% of analytical perchlorate detections are less than 13 µg/L and 42% are less than 6 µg/L.

However, commenters have pointed out limitations of UCMR 1 for estimating current occurrence. The minimum reporting level is 4 µg/L. Since UCMR 1 data has been collected, 2 states have enacted perchlorate standards (CA & MA) and remediation activities or new sources of perchlorate may have impacted concentration levels in public water systems.

Are there any cross-office implications of promulgating a drinking water regulation?
Yes, promulgating a drinking water regulation for perchlorate would become the applicable or relevant and appropriate requirement (ARAR) and would replace the current preliminary remediation goal (PRG) for CERCLA sites (current PRG is based on the Interim Drinking Water Health Advisory level of 15 µg/L).

Is there an Environmental Justice/Equity component for the affected communities?
Each community faces unique challenges when addressing concerns related to environmental issues. Perchlorates in drinking water are related to localized sources of contamination often near where these produced have been manufactured or produced. Currently, if water sampling results confirm that drinking water contains perchlorate at individual or combined concentrations greater than 15 parts per billion, water systems should undertake additional sampling to assess the level, scope and localized source of contamination to inform next steps.

How will the RfD, or the interim health advisory, be used to inform the MCLG?
Based on SAB recommendations EPA does not intend to use the perchlorate RfD to inform derivation of an MCLG. The SAB stated that it, ". . . recognizes that this is a novel approach as compared to previous MCLG derivations that use the RfD and exposure factors. However, PBPK/PDIUI modeling provides a more rigorous tool to integrate the totality of information available on perchlorate, and this approach may better address different life stage susceptibilities to perchlorate than the default MCLG approach."

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Message

From: Hafez, Ahmed [Hafez.Ahmed@epa.gov]
Sent: 1/11/2018 11:08:25 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; El Burai Felix, Alia [ElBuraiFelix.Alia@epa.gov]
Subject: RE: perchlorate comment letter from DoD
Attachments: DoD Comments.pdf; WA459_T3_Public Comments Matrix_180105.xlsx

Hi Eric,

Please find the attached comments from DoD. Also attached is a first-pass comment matrix with our initial informal responses to the public comments. We focused on the approaches and did not develop responses for most of the ORD/BBDR model specific comments.

Let me know if you have any questions.

Regards,
Ahmed

Ahmed M. Hafez, Ph.D.
OW/OGWDW/SRMD/TAB | Office: WJC East 2227Q
hafez.ahmed@epa.gov | phone: 202.564.1944

From: Christ, Lisa
Sent: Thursday, January 11, 2018 5:34 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; El Burai Felix, Alia <ElBuraiFelix.Alia@epa.gov>
Subject: perchlorate comment letter from DoD

When you get a chance, can someone please send the perchlorate comment letter from DOD to Eric Burneson?
Thanks,
L

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 5/30/2017 12:00:19 PM
To: Wadlington, Christina [Wadlington.Christina@epa.gov]
CC: Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: Fwd: MCLG.Perchlorate Roll Out_5.15.17.docx
Attachments: MCLG.Perchlorate Roll Out_5.15.17.docx; ATT00001.htm

Christina
A few comments on the perchlorate comm plan. Let me know if you want to discuss.
Thanks!
Jennifer

Perchlorate Peer Review
Communications Plan

PRE-PUBLICATION RELEASE DATE: Approximate Date, 2017

ACTION: The agency is undertaking an independent, external panel peer review and announces the release of several materials for public comment that relate to the development of a maximum contaminant level goal and a National Primary Drinking Water Regulation for perchlorate.

KEY MESSAGES

- Perchlorate – a chemical used in rocket propellants and other applications – can disrupt the normal function of the thyroid gland in both children and adults.
- EPA is currently determining the appropriate approach for deriving a Maximum Contaminant Level Goal (MCLG) for perchlorate.
- The agency initiated a peer review and is releasing the interim list of peer review candidates, draft charge questions as well as a draft MCLG approach report.
- The MCLG approach report provides information regarding how EPA intends to apply ~~BBDR~~ biological model outputs to the development of the perchlorate MCLG.
- The use of the ~~BBDR~~ biological model and draft approach to inform an MCLG is precedent-setting, therefore EPA is conducting a transparent and rigorous expert peer review process.
- After the peer review is complete, EPA will take the next appropriate steps.

ANTICIPATED REACTION

There is likely to be considerable interest and response to EPA's release of peer review materials and the peer review process itself. Over the past several years, stakeholders have provided extensive comments on publically reviewable perchlorate materials and notices, met with EPA senior officials, managers and staff and have wrote the Administrator numerous letters.

EPA was sued by NRDC for the Agency's failure to issue proposed and final regulatory actions for perchlorate in accordance with the timelines provided in SDWA. The court approved consent decree established a schedule for completing the peer review process (10/18/17) and signature of a proposed (10/31/18) and final rule (12/19/19).

Stakeholders and the press are aware that EPA has been working to implement SAB recommendations and develop a BBDR model and approach to inform development of an MCLG.

Stakeholders response will generally be critical of the ~~highly technical, underlying science to~~BBDR model ~~perchlorate in sensitive lifestages~~ and the ~~novel~~ application of the model output to inform derivation of a perchlorate MCLG.

- Stakeholder groups may state that EPA did not allow adequate time to conduct the scientific peer reviews.
- Industry groups (Perchlorate Study Group, American Chemistry Council); drinking water utilities, the U.S. Chamber of Commerce and the Department of Defense will likely be critical of the ~~underlying science~~model and EPA's application of the model.
- Environmental groups may state that EPA is altering the science to avoid regulation~~will likely be critical of the underlying science~~.
- Consumers, both those using public water systems and private wells, will be concerned about potential health risks from perchlorate.

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Perchlorate Peer Review
Communications Plan

DESK STATEMENT

Ensuring the safety of drinking water for all Americans is a top priority for EPA. The agency remains committed to completing the regulatory process for perchlorate in drinking water. The agency has initiated a peer review and is releasing peer review materials that inform decision making on perchlorate under the Safe Drinking Water Act. The materials include an interim list of peer review candidates, draft charge questions as well as a detailed report describing the approaches EPA developed for the biologically based dose-response model and information regarding how EPA intends to apply modeling to the development of the MCLG. After the peer review is complete, EPA will take the next appropriate steps on perchlorate under the Safe Drinking Water Act.

Background

On January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). This level was determined using a reference based dose response based on the recommendation of the National Research Council (NRC).

In 2011, EPA announced its decision (76 FR 7762) to regulate perchlorate under the Safe Drinking Water Act (SDWA). In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The MCLG is a non-enforceable goal defined under the SDWA as "the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." The MCLG is one of the considerations in developing the enforceable maximum contaminant level (MCL) for a regulated contaminant. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

As recommended by the SAB, the agency, with contributions from Food and Drug Administration scientists, developed a BBDR model to determine under what conditions of iodine nutrition and exposure to perchlorate, that infants and lactating mothers would experience hypothyroxinemia (changes in thyroid gland levels). EPA completed the peer review of the BBDR model, ~~and t~~The report provided by the reviewers ~~can~~ may be found on EPA's website at: https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water.

Legal Deadlines: On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

COMMUNICATIONS MATERIALS

Webpage (link will appear on https://www.epa.gov/dwstandardsregulations/perchlorate) will include:

- Link to public inspection FR notice
- Draft Charge Questions

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Perchlorate Peer Review
Communications Plan

- Interim List of Peer Reviewers
- Draft report on the application of the model to inform the development of a perchlorate MCLG

RELEASE SCHEDULE

-3 days

- OGWDW notification to Regional Contacts
- OPA notification to Regional PADS

-2 days

- OGWDW notification to federal partners (FDA, ATSDR, NIEHS)
- OPA calls to federal agencies' communications

Release Day (when publically available on FR site)

9:00 a.m	Begin head's up calls to stakeholder list below
10:00 a.m	Congressional heads up emails
12:00 p.m	Website goes live – Broader congressional notifications (emails with link to website).
1:00 p.m	Social media and stakeholder notification via email (Water Headlines listserv)

STAKEHOLDER NOTIFICATION

OGWDW:

Commented [MJ1]: RCAP

- Michael Deane, Director, National Association of Water Companies
- Tracy Mehan, Government Affairs Director, American Water Works Association
- Mike Paque, Executive Director, Groundwater Protection Council
- Jim Taft, Executive Director, Association of State Drinking Water Administrators
- Lynn Thorp, National Campaigns Director, Clean Water Action
- Diane Van de Hei, Executive Director, Association of Metropolitan Water Agencies
- Sam Wade, Executive Director, National Rural Water Association

OGC:

- Eric Olson/Mae Wu, Natural Resources Defense Council

OLEM (OSRTI):

- Association of State and Territorial Solid Waste Management Officials

EXTERNAL QUESTIONS AND ANSWERS

CONSUMER QUESTIONS

Where is perchlorate found?

Perchlorate occurs naturally in arid states in the Southwest United States, in nitrate fertilizer deposits in Chile, and in potash ore in the United States and Canada. It also forms naturally in the atmosphere. Perchlorate is manufactured and used as an industrial chemical and can be found in rocket propellant, explosives, fireworks and road flares. It has been found in some public drinking water systems and in food.

Why is perchlorate in drinking water a health concern?

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Perchlorate Peer Review
Communications Plan

Perchlorate can disrupt the normal function of the thyroid gland in both children and adults. In adults, the thyroid plays an important role in metabolism, making and storing hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. In fetuses and infants, thyroid hormones are critical for normal growth and development of the central nervous system. Perchlorate can interfere with the human body's ability to absorb iodine into the thyroid gland which is a critical element in the production of thyroid hormones.

How does perchlorate get into my drinking water?
Perchlorate is dissolves easily, is relatively stable and is mobile in water. While it has often been detected in water supplies in close proximity to sites where solid rocket fuel is manufactured or used, there are also many locations in the United States lacking a clearly defined source.

Besides drinking water, how else can people be exposed to perchlorate?
People are exposed to perchlorate primarily through eating contaminated food or drinking water. The Food and Drug Administration (FDA) Total Diet Study combines nationwide sampling and analysis of hundreds of food items along with national surveys of food intake to develop comprehensive dietary exposure estimates for a variety of demographic groups in the U.S. In the 2008-2012 survey the FDA found detectable levels of perchlorate in 97 percent of the foods sampled. The complete set of FDA perchlorate data can be found here:
[HYPERLINK "https://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077615.htm"]

Have public drinking water systems been sampled for perchlorate?
Customers served by a public water system can contact their local water supplier and ask they test for perchlorate. If so, they are encouraged to obtain a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state standards or guidelines. If you are concerned about the possibility of perchlorate in your drinking water and you are served by a private well, EPA recommends testing your drinking water. In addition, EPA recommends that residents reach out to their local public health department for more information.

Commented [MJ2]: Should this be "ask if they test"? These two sentences are confusing to me.

Commented [MJ3]: This is redundant with the response to the next question (and tangential to this question)

The most recent Consumer Confidence Report can be obtained from your drinking water utility, by visiting their website or contacting them for a copy. Some public water systems upload their Consumer Confidence Report to EPA's website at: [HYPERLINK "http://www.epa.gov/ccr" \h]. Information about private wells can be found here: [HYPERLINK "http://www.epa.gov/privatewells" \h].

Also, if your public water system participated in collecting monitoring data for UCMR 1, you can find information about your system at: [HYPERLINK "https://www.epa.gov/dwucmr/first-unregulated-contaminant-monitoring-rule"].

I live in a community with elevated perchlorate levels. Who do I call to get more information about what my utility is doing to address the elevated levels?
Contact your local water supplier to find out more about perchlorate in your drinking water. If you don't know who your local water supplier is, the information should be included in your latest water bill.

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Perchlorate Peer Review
Communications Plan

I get my tap water from a private well. How can I find out if perchlorate are in my water?
If you are concerned about the possibility of perchlorate in your drinking water and you are served by a private well, EPA recommends testing your drinking water. Approved laboratories can analyze a sample of your water to determine whether perchlorates are present and at what concentrations. Your local water or health department or drinking water system should know if there is such a program in your area. In addition, EPA recommends that residents reach out to their local public health department or state who may be able to help provide support for testing or to seek such support from a responsible party. If no program has been established or support is not available in your area, you can pay to have independent testing done at a qualified testing lab (typical cost is several hundred dollars per sample).

More information about private wells can be found here: [HYPERLINK "http://www.epa.gov/privatewells" \h].

Can a person drink tap water containing perchlorate at or below the level of the health advisory every day of their life and not expect adverse health effects from these chemicals?
Yes, the EPA health advisory level offers a margin of protection for all Americans from adverse health effects for a lifetime of exposure to perchlorate in drinking water at 15ppb.

Can perchlorate be boiled out of my water?
No, perchlorate cannot be removed by heating or boiling water.

Should I be worried about reconstituting my child's infant formula with tap water?
Refer to FDA

Should I consider taking iodine dietary supplements if I am worried about perchlorate?
Refer to FDA

Commented [MJ4]: I'm not sure why FDA would be the contact for either of these questions.
If they are the correct contact, have we coordinated with them so they are prepared to respond?

How does a utility reduce/remove perchlorate?
A number of options are available to drinking water systems to lower concentrations of perchlorate in the drinking water supply. In some cases, drinking water systems may be able to reduce concentrations of perchlorate by closing contaminated wells or changing rates of blending of water sources. Perchlorate can be removed using a number of advanced treatment techniques. Each technique has advantages and disadvantages depending on the level of perchlorate present in the source water, removal goals, other water quality parameters, competing treatment objectives, and treatment waste disposal options. Regenerable and single-pass ion exchange, reverse osmosis, and fixed- and fluidized-bed biological treatment can all remove perchlorate from drinking water sources.

These treatment systems are used by some public water systems today, but should be carefully designed and maintained to ensure that they are effective for treating perchlorate.

Home drinking water treatment units are typically certified by independent third party organizations against ANSI (American National Standards Institute) standards to verify their contaminant removal claims. Some home filters remove impurities using reverse osmosis; however, there currently are no ANSI protocols for testing home treatment systems to verify that these devices effectively remove perchlorate or how frequently the filters should be changed in order to maintain removal efficiency.

Commented [MJ5]: This doesn't seem to fit with the question

Can I buy a home treatment device to remove perchlorate?

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Perchlorate Peer Review
Communications Plan

If you are concerned about perchlorate in your drinking water, you may consider purchasing a home treatment device such as a filter. However, in order to make a well-informed and cost-effective decision, consider checking with your water system or consumer confidence report to learn about the amount of total perchlorate in your water and identifying a device that has been independently certified to remove perchlorate.

[HYPERLINK "http://www.nsf.org/consumer-resources/what-is-nsf-certification/water-filters-treatment-certification/contaminant-reduction-claims-guide" \t "_blank"], the [HYPERLINK "https://www.wqa.org/" \t "_blank"], [HYPERLINK "http://ul.com/" \t "_blank"] and [HYPERLINK "http://www.csagroup.org/global/en/services/testing-and-certification" \t "_blank"] all certify home treatment products for removal of contaminants. The relevant perchlorate removal standard is [HYPERLINK "http://www.nsf.org/consumer-resources/health-and-safety-tips/water-quality-treatment-tips/standards-for-water-treatment-systems" \t "_blank"]. If you choose to use a home treatment device, it is very important to follow the manufacturer's operation and maintenance instructions carefully in order to make sure the device works properly.

Commented [MJ6]: These 2 responses about home treatment are inconsistent with eachother.

Does perchlorate have a health advisory level?
Yes, on January 8, 2009, EPA released an interim drinking water health advisory of 15 parts of perchlorate for every billion parts of water (parts per billion or ppb). ~~For~~ More information on the Interim Drinking Water Health Advisory for perchlorate can be found here: [HYPERLINK "http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.txt"]

Has a safe level of exposure for perchlorate been established?
On February 11, 2011, EPA determined that perchlorate meets the Safe Drinking Water Act criteria for regulation as a contaminant. The Agency found that perchlorate may have an adverse effect on the health of persons and is known to occur in public drinking water systems with a frequency and at levels that present a public health concern. Since that time, EPA has been reviewing the best available scientific data on a range of issues related to perchlorate in drinking water including its occurrence, treatment technologies, analytical methods and the costs and benefits of potential standards.

There also have been state actions on perchlorate standards, guidelines, and advisories. In 2006, Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L, and in 2007, California promulgated a standard of 6 µg/L. Twelve other states have established non-enforceable guidance levels, action or advisory levels. Depending on the state, a particular level may require a public water system to notify the public, serve as a screening tool for further action, or guide clean-up actions.

Customers that are served by a public water system can contact their local water supplier and ask for information on perchlorate in their drinking water, and are encouraged to request a copy of their Consumer Confidence Report. This report lists the levels of contaminants that have been detected in the water, including those by EPA, and whether the system meets state and EPA drinking water standards.

PEER REVIEW QUESTIONS

Why is EPA conducting a peer review?
EPA will ask peer reviewers to comment on products that the agency will use to inform decision making on perchlorate under the Safe Drinking Water Act

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Perchlorate Peer Review
Communications Plan

EPA believes that peer review is an important component of the scientific process. The critical feedback, suggestions, and new ideas provided by the peer reviewers stimulate creative thought, strengthen the interpretation of the reviewed material, and confer credibility on the product. The peer review objective is to provide advice to EPA on steps that will yield a highly credible scientific product that is supported by the scientific community.

What products will be reviewed?
Peer reviewers will be asked to comment on the draft report entitled "Peer Review Draft: Proposed Approach to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water." ~~Additionally,~~ EPA is seeking public comments on this report and also on the peer review charge and the interim list of expert peer review panel candidates.

Where can I find the review products?
All documents in the docket are listed on the [HYPERLINK "http://www.regulations.gov"] website under Docket ID Numbers EPA-HQ-OW-2016-0438 and EPA-HQ-OW-2016-0439.

Can I provide comments on the review products?
Yes. The public will have an opportunity to review and comment on the draft charge questions, the interim list of peer reviewers and the draft report describing application of the model to inform development of a perchlorate MCLG.

Additionally, we intend to allow for people to make brief statements during the meeting, and any Safe Drinking Water Act regulation on perchlorate will be subject to public notice and comment.

How long is the comment period?
EPA announced that it is seeking public comments on two separate sets of materials. The first set is the interim list of peer review candidates and the draft charge questions. People should send their comments to Versar, Inc. no later than 21 days after publication in the Federal Register.

A companion notice, also published on the same date, requests comments on the draft report on application of the model to inform derivation of a perchlorate MCLG. People should send their comments to the docket no later than 45 days after publication in the Federal Register.

Will the review panelists see my comments or just EPA?
EPA will provide panelists a summary of the public comments submitted on the draft products.

When and where will EPA hold the meeting?
The meeting is projected to occur during in the fall of 2017 (exact date to be determined). EPA will announce the meeting in the Federal Register at least 30 days in advance to provide the meeting date, location and registration information. EPA anticipates holding the two-day meeting in the Washington, DC metro area.

What will EPA do with the public comments and panel recommendations?
A peer review summary report will be developed that contains the final comments and recommendations from the peer reviewers. EPA will make the final peer review report available to the public.

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EPA will consider any public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the documents.

How will the contractor select the reviewers?
The contractor considered and screened all candidates against the selection criteria described in the March 1, 2016, and June 3, 2016, Federal Register notices (81 FR 10617 and 81 FR 35760, respectively) which included being free of any conflict of interest and being available to participate in-person in the peer review meeting.

Following the screening process, the list was narrowed to 12 candidates. EPA is now soliciting comments on the interim list of 12 candidates. Once the public comments on the interim list of candidates have been reviewed and considered, and the Science Integrity Official has been consulted, the final list of peer reviewers will be selected.

What happens next?
Once the public comments on the interim list of candidates have been reviewed and considered, the final list of peer reviewers will be selected.

What happens after the peer reviewers are selected?
Following the selection process, the peer reviewers will be tasked with evaluating and providing written comments on the draft products. Additionally, peer reviewers will be provided a summary of public comments and given access to public comments submitted during the draft document's public comment period.

When will EPA establish a national drinking water standard for perchlorate?
EPA will to consider public comments and peer reviewer comments submitted in accordance with the Federal Register notice when finalizing the ~~peer review products~~materials that inform decision making on perchlorate under the SDWA. After the peer review is complete, EPA will take the next appropriate steps on perchlorate under the SDWA.

INTERNAL QUESTIONS AND ANSWERS

Why is it taking so long for us to regulate perchlorate?
In 2011, EPA announced its decision to regulate perchlorate under the Safe Drinking Water Act (SDWA).

In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to review how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a perchlorate National Primary Drinking Water Regulation. The SAB released its final report on May 29, 2013 and recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling."

The agency, with contributions from Food and Drug Administration scientists, spent over two years to develop the model that accounts for population differences in iodide exposure and predicts changes in thyroid hormone levels that result from exposure to perchlorate.

Commented [MJ7]: Three?

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Perchlorate Peer Review
Communications Plan

What is the status of the NRDC complaint? (CLEAR WITH OGC)
On February 18, 2016, the Natural Resource Defense Council filed a complaint for the Southern District of N.Y., alleging that EPA failed to perform a nondiscretionary duty under SDWA to propose and finalize a national primary drinking water regulation for perchlorate. On October 18, 2016, the court approved a consent decree establishing dates for –

- completing the peer review process (10/18/17, non-enforceable);
- filing a peer review status report (10/30/17); and
- signature of a proposed and final rule (10/31/18 and 12/19/19, respectively).

Will the peer review products present alternative MCLGs?
No, the documents will not present alternative MCLGs, however some experts can be expected to predict the MCLGs that would result from using the methodologies that are described in the documents.

Will the methodologies that will be presented to the peer reviewers result in MCLGs that are in the range of MCLs set by California (6 µg/L) and Massachusetts (2 µg/L)?
Yes. Additionally, 12 states have guidance levels: AZ, FL, IL, KS, MD, NV, NJ, NM, NY, OR, TX, VT. The drinking water levels range from 1 to 18 µg/L. These levels may trigger public notice, serve as a screening tool for further action or guide cleanup action.

Commented [MJ8]: Is this correct?

What is our evaluation of perchlorate occurrence data?

The UCMR 1 perchlorate dataset is the best available nationally representative data on perchlorate occurrence in public water systems. Analytical detections of perchlorate at or above the minimum reporting level (4 µg/L) were identified in about 4% (155 of 3,865) of these systems. EPA estimates that between 5.1 million to 16.6 million people served by the sampled systems could be exposed to perchlorate in drinking water. While perchlorate analytical detections are fairly numerous and widespread geographically, the UCMR 1 findings indicate that perchlorate occurs at relatively low levels: about 85% of analytical perchlorate detections are less than 13 µg/L and 42% are less than 6 µg/L.

However, commenters have pointed out limitations of UCMR 1 for estimating current occurrence. The minimum reporting level is 4 µg/L. Since UCMR 1 data has been collected, 2 states have enacted perchlorate standards (CA & MA) and remediation activities or new sources of perchlorate may have impacted concentration levels in public water systems.

Are there any cross-office implications of promulgating a drinking water regulation?
Yes, promulgating a drinking water regulation for perchlorate would become the applicable or relevant and appropriate requirement (ARAR) and would replace the current preliminary remediation goal (PRG) for CERCLA sites (current PRG is based on the Interim Drinking Water Health Advisory level of 15 µg/L).

Is there an Environmental Justice/Equity component for the affected communities?
Each community faces unique challenges when addressing concerns related to environmental issues. Perchlorates in drinking water are related to localized sources of contamination often near where these produced have been manufactured or produced. Currently, if water sampling results confirm that drinking water contains perchlorate at individual or combined concentrations greater than 15 parts per billion, water systems should undertake additional sampling to assess the level, scope and localized source of contamination to inform next steps.

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How will the RfD, or the interim health advisory, be used to inform the MCLG?
Based on SAB recommendations EPA does not intend to use the perchlorate RfD to inform derivation of an MCLG. The SAB stated that it, ". . . recognizes that this is a novel approach as compared to previous MCLG derivations that use the RfD and exposure factors. However, PBPK/PDIUI modeling provides a more rigorous tool to integrate the totality of information available on perchlorate, and this approach may better address different life stage susceptibilities to perchlorate than the default MCLG approach."

ED_005043_00057890-00010

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 3/22/2017 2:48:55 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: RE: Notes on LCR and Perchlorate
Attachments: 1 pager perchlorate in drinking water.doc

Here's the perchlorate 1 pager…

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 10:25 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notes on LCR and Perchlorate

Here is a draft of the LCR one pager. Take a look to confirm its accuracy and use as a model for your perchlorate paper.

From: Christ, Lisa
Sent: Tuesday, March 21, 2017 5:20 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Notes on LCR and Perchlorate

Here are the schedules -

From: Gonzalez, Yvonne V.
Sent: Tuesday, March 21, 2017 3:16 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Notes on LCR and Perchlorate

Eric and Lisa,

Ann's looking to get a couple of notes (one-pager) on the LCR and Perchlorate schedules Mike could send to the political team ahead of scheduling meetings? I know we have an LCR revisions weekly coming up – but can we turn something around to them as soon as possible? I believe the OW weeklies on the LCR nominations have triggered some folks. Please advise.

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN

Purpose: To improve the health protection to drinking water consumers from perchlorate.

Background: On February 11, 2011 (76 FR 7762), EPA announced its decision to regulate perchlorate based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant.

- SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013) and finalize the regulations 18 months after proposal (can extend up to 9 months).
- In early 2012, EPA sought recommendations from SAB on how to derive a Maximum Contaminant Level Goal for perchlorate in accordance with SDWA.
- The SAB May 29, 2013 report recommended that EPA "derive a perchlorate MCLG[1] that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling (PBPK)."
- In response to SAB recommendations, FDA and EPA scientists worked collaboratively to develop Biologically Based Dose Response (BBDR) models to relate perchlorate exposure to biological effects to infants, the other key lifestages. An expert peer review of the models has been completed and we are preparing for a subsequent expert peer review of approaches to apply the model output (change in thyroid hormones during pregnancy) to neurodevelopmental outcomes in children.

Stakeholder Involvement: There is likely to be considerable interest and response to EPA's release of peer review materials and the peer review process itself. Over the past several years, stakeholders have provided extensive comments on publically reviewable perchlorate materials and notices, met with EPA senior officials, managers and staff and wrote the Administrator numerous letters. Industry groups (Perchlorate Study Group, American Chemistry Council), environmental groups, drinking water utilities, the U.S. Chamber of Commerce and the Department of Defense will likely be critical of the underlying science. Consumers, both those using public water systems and private wells, will be concerned about potential health risks from perchlorate.

Key Issues/Internal Review: EPA was sued by Natural Resource Defense Council for the Agency's failure to issue proposed and final regulatory actions for perchlorate in accordance with SDWA timelines.

Legal Deadlines: Through a consent decree, the court established enforceable dates of October 31, 2018 for signature of a proposed rule for publication in the federal register and a signature date of December 19, 209 for the finale rule.

Timing: In order to complete necessary analyses for development of a proposed rule, including the Heath Risk Reduction Cost Analysis required by SDWA, we will need to initiate expert peer review of the approaches to derive an MCLG in mid May and complete the review in October 2017. We would like to brief the A.O. in April.

---

[1] Maximum Contaminant Level Goal (MCLG) is a non-enforceable public health goal. The enforceable standard, the Maximum Contaminant Level (MCL) The MCL is set as close to the MCLG as feasible taking cost into consideration.

Message

From: Lavoie, Emma [Lavoie.Emma@epa.gov]
Sent: 11/22/2017 2:52:53 AM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]
Subject: RE: AWWA perchlorate MCLG comments_11.20.17.pdf
Attachments: AWWA perchlorate MCLG comments_11.20.17.pdf

Hi Eric

What will be the process for addressing these comments, e.g., timing and your needs for our input?
Including Paul and Dustin so they can take a look.

-Emma

Tel: 202 564 7091

From: Burneson, Eric
Sent: Monday, November 20, 2017 5:07 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: FW: AWWA perchlorate MCLG comments_11.20.17.pdf

Sharing AWWA's comments on the perchlorate peer review document.

From: Kevin Morley [mailto:KMorley@awwa.org]
Sent: Monday, November 20, 2017 4:33 PM
To: Shapiro, Mike <Shapiro.Mike@epa.gov>
Cc: Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tracy Mehan <tmehan@awwa.org>; svia@awwa.org
Subject: AWWA perchlorate MCLG comments_11.20.17.pdf

Please accept the attached comments from AWWA regarding the proposed MCLG approach for perchlorate.

Sent on behalf of G. Tracy Mehan, III.

Kevin M. Morley, PhD
American Water Works Association
Manager, Federal Relations
1300 Eye Street, NW Suite 701W
Washington, DC 20005
D: 202-326-6124

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November 20, 2017

SUBMITTED VIA E-MAIL

Mr. Michael H. Shapiro
Acting Assistant Administrator
USEPA, Office of Water
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

RE: Comments on the draft Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438)

Dear Mr. Shapiro:

The American Water Works Association (AWWA) appreciates the opportunity to review and comment on the Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal (MCLG) for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438).

We recognize and support EPA's efforts to address the recommendations made by the Science Advisory Board in 2013. Our review of the proposed MCLG approach and biologically based dose-response (BBDR) modeling for perchlorate has identified several areas of concern that should be considered closely by the Agency and the selected peer reviewers. A detailed assessment is attached, but in general terms the results of our review yielded the following overall conclusions:

1. The BBDR is not capable of adequately predicting iodine uptake or free thyroxine (fT4) based on attempts to simulate multiple key studies measuring perchlorate inhibition of iodine uptake, which is a necessary precursor to thyroid effects.
2. Several modeling assumptions are not appropriately documented or are based on insufficient data. This results in increased uncertainty associated with the scientific integrity of the model required to support the proposed MCLG approach.
3. EPA's process for selecting key studies linking changes in fT4 levels and neurodevelopmental effects in the proposed MCLG approach was (a) not transparent

and (b) introduced additional uncertainty, especially when confounding variables (e.g., hCG, iron deficiency) are not controlled.

In summary, while EPA's efforts to address the SAB recommendations are laudable, we believe the proposed approach contains significant uncertainties and is, therefore, insufficient for supporting a risk assessment. Until the uncertainties in the current MCLG approach can be addressed, EPA should continue to rely on the RfD recommended by the National Academy of Sciences for considering further regulatory action. The results of the modeling simulation we prepared for this review of the MCLG approach confirmed the conclusions of prior studies that low levels of perchlorate have no demonstrated health consequence that can be scientifically validated with the confidence necessary to support the proposed MCLG approach.

Should you have questions or would like to discuss this matter, please contact me (tmehan@awwa.org) or Kevin Morley (kmorley@awwa.org).

Sincerely,

G. Tracy Mehan, III
Executive Director – Government Affairs

cc: Peter Grevatt – EPA/OW/OGWDW
Eric Burneson – EPA/OW/OGWDW/SRMD
Samuel Hernandez – EPA/OW/OGWDW/SRMD

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Prepared for
The American Water Works Association

Date
November 2017

By
Robinan Gentry, PhD, DABT
Tracy Greene, BS
Ramboll Environ US Corporation, Monroe, Louisiana

Harvey J. Clewell, III, PhD, DABT, FATS
C. Eric Hack, MS
ScitoVation, Research Triangle Park, North Carolina

COMMENTS ON USEPA 2017:

"PROPOSED APPROACHES TO INFORM THE DERIVATION OF A MAXIMUM CONTAMINANT LEVEL GOAL FOR PERCHLORATE IN DRINKING WATER"

RAMBOLL ENVIRON

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EXECUTIVE SUMMARY

The document provides comments on the US Environmental Protection Agency's (USEPA) 2017 report entitled "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", which was prepared by the USEPA's Office of Ground Water and Drinking Water (USEPA 2017). In this report, USEPA (2017) is proposing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate in accordance with recommendations made from previous reviews conducted by the USEPA's Science Advisory Board (SAB). This MCLG approach (USEPA 2017) includes revisions to a previously developed and peer reviewed biologically-based dose-response (BBDR) model that has been extended to predict the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages. These revisions, suggested by the SAB (2013), include the following:

- Derivation of a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling;
- Expansion of the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilization of a mode of action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; and
- Extension of "the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB 2013, p. 19).

USEPA's (2017) attempts to address SAB's recommendations should be applauded. Revisions presented in the report include methods that extend the model to early pregnancy and incorporate biological feedback control of hormone production via TSH signaling, adding a description of the impact of lower levels of iodide nutrition. In addition, an attempt has been made to calibrate the model's behavior for upper and lower percentiles of the population, as well as the population median for thyroid hormone production. Finally, an uncertainty analysis for key parameters was conducted.

For the development of the MCLG, USEPA has proposed a two-stage approach linking the revised BBDR model results ("Stage 1") with quantitative information on neurodevelopmental outcomes from epidemiological studies ("Stage 2"). Stage 1 describes the thyroidal hormone levels in women of childbearing age with low to adequate iodide intake. In this stage, the revised BBDR model is applied to predict the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. Data for Stage 2 of the approach is provided from epidemiological studies evaluating maternal thyroid hormone levels in early pregnancy and the relationship between changes in these levels and the observation of neurodevelopmental outcomes. USEPA (2017) has also developed an alternative population-based approach that uses the revised BBDR model to estimate changes levels of selected thyroid hormones, specifically free T4, resulting from perchlorate exposure that may result in a shift in the population of hypothyroxinemic pregnant women.

Following a review of USEPA (2017), comments were prepared and organized around three main topics:

- USEPA model revisions including those for extending the model to early pregnancy, incorporating biological feedback control of hormone production via TSH signaling, calibrating the model and evaluating its behavior, and conducting an uncertainty analysis for key parameters. This includes comparison of model output to results from key studies, including

those identified in previous assessments, including results reported by Greer et al. (2002), Braverman et al. (2006), and Téllez Téllez et al. (2005a, 2005b);

- Linking BBDR results to neurodevelopmental outcomes focusing on the identification of published literature to develop the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes; and
- Comparison of the results from the BBDR modeling and MCLG approach with results and key studies from previous USEPA assessments.

The results of our review of the EPA's proposed MCLG approach (EPA 2017) and BBDR modeling for perchlorate yielded the following overall conclusions:

- While we applaud the EPA for the application of a BBDR model in the MCLG approach, as these models integrate the available science for a compound of interest, there is some concern that uncertainties inherit in the model call into question its proposed application in the risk assessment for perchlorate and whether it is fit for that purpose. While the hormone component of the model is a definite scientific improvement in terms of incorporating the available biology, there is a lack of data to provide validation of multiple steps in the proposed approach and of the assumptions/parameters within the biologically based dose-response (BBDR) model.
- Many of the changes in free thyroxine (fT4) that are predicted by the MCLG approach to impact the population distribution of fT4 and therefore result in per unit changes in neurodevelopmental outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to suggest that the extended version of the BBDR model has a capability to estimate small changes in fT4 with precision that is not demonstrated by any adequate validation. Further, the model predictions of fT4 underpredict observed data in various clinical studies by substantially more than 1.3-4.3%. This suggests that the model is not precise enough to predict such small changes in fT4. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as to whether these slight changes could be measured clinically, considering the greater impact of iodine intake on hormone levels.
- Until additional data are available to validate current extensions of the BBDR model to the pregnant woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake and, therefore, impacts on fT4. Based on recommendations from the National Research Council (2005), points of departure provided by these studies used in combination with uncertainty factors were considered to be protective of sensitive subpopulations, and provides a basis for future risk management decisions.

Therefore, we conclude that while the MCLG approach as proposed by USEPA incorporates additional science into the process, it still contains significant uncertainties that call into question the use of this approach to support a regulatory decision. Until the uncertainties in the current MCLG approach can be addressed, USEPA should continue to rely on the RfD recommended by the NAS for considering further regulatory action.

1. MODEL REVISIONS

1.1 Extending the Model to Early Pregnancy

The MCLG approach (USEPA 2017) is based on a hypothesized mode of action for neurodevelopmental outcomes associated with the development of hypothyroxinemia as a result of perchlorate exposure. The sensitive populations of concern for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women. Extending the model to predict the impact of perchlorate exposure on fT4 during early pregnancy is complicated by the significant variability in the levels of fT4 in the general population and the challenges in measuring fT4, as well as by the uncertainty in the identification of an alteration that may over time change fT4 from an individual's "set-point" and therefore potentially impact circulating levels in both the mother and the fetus.

According to the "American Thyroid Association Task force on Thyroid Disease During Pregnancy and Postpartum", isolated hypothyroxinemia is defined as a normal maternal TSH concentration in conjunction with fT4 concentrations in the lower 5th or 10th percentile of the reference range (Stagnaro-Green et al. 2011). USEPA (2017) has also focused on selected percentiles of the reference range; however, reference ranges can vary from population to population (Alexander et al. 2017). Even within US populations and across ethnic groups, the 2.5th percentile can vary by up to 2 pmol/L or approximately 20% (9.3-11.4 pmol/L as reported by Alexander et al. (2017)).

The variation in fT4 reported in the published literature during early pregnancy is provided in USEPA (2017), Appendix A, Figure A-33. The levels of fT4 during early pregnancy, based on the studies identified by USEPA (2017), appear to range from approximately 12-16 pmol/L. This range is consistent with the range of fT4 means reported in the Greer et al. (2002) study at baseline of approximately 1.2 ng/dL (15.5 pmol/L). However, the 50th percentile model predictions at zero dose perchlorate and 170 µg/day iodine intake (approximately 10 pmol/L at gestation weeks 12, 13, and 16) are much lower than these reported values.

Measuring fT4 in the presence of high concentrations of bound T4 is challenging, especially in conditions where binding proteins are altered such as during pregnancy (Alexander et al. 2017). Measurement techniques are prone to inaccuracy during pregnancy due to disruption of the original equilibrium. The 95% fT4 reference intervals decrease gradually with advancing gestational age: from 1.08– 1.82 ng/dL (approximately 13.9 – 23.5 pmol/L) in week 14 to 0.86–1.53 ng/dL (approximately 11.1 – 19.8 pmol/L) in week 20.

In addition, as noted in USEPA (2017):

> *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see Figure 2) that operates around a "set-point." This set-point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance (Andersen, Pedersen, Bruun, & Laurberg, 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations (Andersen et al. 2002)."*

Extending the thyroid BBDR model to address early gestation is a significant challenge due to the complex interaction between thyroid homeostasis and gestational development. While the model appears to accurately simulate average fT4 in early gestation in the absence of perchlorate exposure, (Figure A57 in Appendix A), a previous peer review panel noted that

the model of early 2017 was most appropriate for higher iodide and lower or zero perchlorate exposures. Considering the addition of TSH feedback dynamics, and an adjustment factor to match specific population percentiles, there is reason for concern regarding the uncertainty of the revised model predictions under low iodide intake conditions. Some of these concerns are highlighted below:

- In addition to regulation by TSH, hCG levels rise in early pregnancy and this increases NIS uptake activity and T4 production. hCG is structurally similar to TSH, and stimulates iodide transport and thyroid hormone synthesis through stimulation of the TSHR. In the model, the Vmax for NIS-mediated uptake is increased during pregnancy based on independent data, but that change is not described as a function of hCG. "VmaxNISF_thy_I is scaled to increase with pregnancy based on an empirical relationship between gestational age and radioactive iodide uptake." hCG is calculated as a function of gestational age, and is then used to increase T3 and T4 production, but the increase in thyroidal iodine uptake is mistakenly ascribed by the model to TSH. This suggests that the model structure is not true to the biology, introducing uncertainty to predictions of T4 during pregnancy.
- The current model uses a baseline first-order constant calibrated to NHANES 2007-2012 median, 10th, or 90th percentile non-pregnant data. The KProdT4F value for the median NHANES calibration is 6.25*10-7 /hr/kg$^{0.75}$ (Table A-2), which is lower than 2.45 x 10-6 used by Lumen et al. (2013) based on fitting to data of Nicoloff et al. (1972). This value is scaled in pregnancy with increasing KProdT4 through GW 16 (peak occurring ~ GW 9) based upon placental hCG increase over this time according to the linear relationship from Glinoer (1997): hCGreg = 1 + 0.00354 x hCG. However, the use of a T4 production rate that is lower than the published value is not adequately justified, given the importance of this parameter, which has a direct impact on predictions of fT4 changes, for the intended application of the model.
- The current model uses a Km for perchlorate binding to the NIS (KmNIS_P) that is 3-fold lower than Lumen et al. (2013) (i.e. a 3-fold higher affinity). Specifically, Km is the 2.5th percentile lower confidence limit of the population median based upon USEPA reanalysis of Greer et al. (2002). The value (50th percentile = 0.73 μM) is similar to that obtained from re-analysis of in vitro binding data, 0.59 μM (Schlosser 2016); use of KmNIS_P = 0.489 μM makes perchlorate 3 times more effective at competitive inhibition of NIS versus Lumen et al. (2013).
- Plots of NHANES 2007-2012 data for non-pregnant women demonstrated little relationship between iodine intake and fT4, even at iodide intake levels below 75 μg/day (Figure A-54). Given limited data in this range, USEPA has used the relationship between thyroidal iodide stores (mg) and iodine intake, which shows depletion of fT4 at iodide intake levels below 100 μg/day (Delange, 2000). It is clear from Figure A-54, this is inconsistent with the NHANES data. This relationship was used as part of a parameter calibration procedure to simulate population percentiles of fT4, T4, T3, and TSH identified from NHANES data (see Appendix A, Figures 54-56)." However, script files included with the BBDR model use an iodine intake of 90 μg/day. The model is much more sensitive to iodine intake than perchlorate dose, with minimal changes to hormone levels due to perchlorate exposure at high iodine intake levels. The various iodine intake levels used for model simulations need to be more clearly presented and justified.

1.2 Calibrating the Model and Evaluating its Behavior

In development of these comments, multiple studies were independently simulated to an attempt to duplicate datasets that were reported by USEPA (2017) to calibrate the model. This included studies

to evaluate the model's behavior and determine if the results were consistent with the final values reported in the draft MCLG approach. This included:

- Comparison to the Steinmaus et al. 2016 results
- Other key studies noted in previous assessments:
  - Greer et al. 2002 – 14 day worker study
  - Braverman et al. 2006 – 6 month study
  - Téllez Téllez et al. 2005a, 2005b – Chile study (see attached)

In efforts to produce these simulations, it was noted that instructions for running the model for different scenarios, and documentation of the rationale for the model parameter values associated with them, are inadequate and lack transparency; this deficiency is exacerbated by the number of permutations of parameter settings used to generate the figures in the document. As a result it is difficult to have confidence in the results of a model evaluation, even by an experienced modeler, due to the significant uncertainties regarding the steps necessary to reproduce the figures and tables in the report, or to perform comparisons of model predictions to data for alternative exposure scenarios or studies.

1.2.1 Comparison to the Steinmaus et al. 2016 Results

In Appendix B of USEPA (2017), a comparison of the predicted changes in both fT4 and TSH from the BBDR model were compared to the results reported by Steinmaus et al. (2016). The Steinmaus et al. (2016) study was conducted to evaluate the potential for perchlorate exposure to impact thyroid hormone levels in pregnant women in San Diego. They reported an effect of perchlorate on fT4 levels to be similar among women with both low iodine (<100 µg/day) and normal (100-300 µg/day), with a greater effect of perchlorate observed among pregnant women in the high iodine intake group (>300 µg/day). They noted that this effect has been observed in NHANES evaluations

The comparison of the predicted fT4 changes from the BBDR model and the Steinmaus et al. (2016) results associated with changes in perchlorate dose are reported in Figure B-1. Duplication of this BBDR modeling output was possible using the USEPA provided modeling code, with additional instruction from USEPA staff. However, this comparison clearly highlights the differences between the model predictions and those from a published study. The baseline simulations with normal iodine intake (170 µg/day) demonstrate no change in fT4, which is consistent with other studies in which no impact on fT4 has been observed at doses up to 7 µg/kg/day (Greer et al. 2002; Braverman et al. 2006). The model underpredicts the changes in fT4, even in the scenario with low dietary iodine intake (75 µg/day), in comparison to the changes reported by Steinmaus et al. (2016). This discrepancy demonstrates the significant uncertainty in the ability of the model to predict changes in fT4 associated with perchlorate exposure. In particular, the current MCLG approach results in small changes in fT4 as low as approximately 1% being predicted to result in unit changes in neurodevelopmental endpoints. Predictions of this precision would require a level of model precision that has not been demonstrated by comparison to existing data.

1.2.2 Other Key Studies Noted in Previous Assessments:

Greer et al. 2002 – 14 day study

The Greer et al. (2002) study was conducted to establish the dose-response in humans for perchlorate inhibition of thyroidal iodide uptake and any short-term effects on thyroid hormones following exposure for male and female volunteers to perchlorate in drinking water at doses of 7, 20, 100 or 500 µg/kg/day for 14 days. The results of this study have previously been relied upon by the USEPA (2005) to derive a reference dose (RfD) and to determine health reference levels (HRLs). The results of this study indicate a decrease in iodide uptake following exposure to a dose of 20

µg/kg/day, but no effect on hormone levels, including fT4 and TSH, at the highest dose tested. A No Observed Effect Level of 7 µg/kg/day was determined based on these results, and an RfD of 0.7 µg/kg/day was adopted, based on NRC recommendations, with the application of an uncertainty factor of 10 for intraspecies variability or sensitive subpopulations.

Consistent with the results of the study, simulating the exposure of the Greer et al. (2002) with the BBDR model indicated no significant change in fT4 at doses up to 500 µg/kg/day. However, predicted concentrations of fT4 are lower than those measured by Greer et al. 2002. The model simulation was run with an iodine intake of 90 µg/day, as this was the value USEPA used in the Greer_test.m script. However, 90 µg/day is not consistent with the 170 µg/day value EPA reports as representing a sufficient intake and USEPA's documentation does not indicate why a lower value was used for the individuals in the Greer study. Simulation of iodide uptake inhibition (RAIU) appears to over-predict the measured values, though the qualitative increasing trend of inhibition with dose behaves appropriately. This discrepancy may result from the low iodine intake chosen by USEPA.

Table 1. Simulation of the Greer et al. (2002) Perchlorate Study

Dose	RAIU (%)		fT4 (pM)	
(ug/kg/d)	Simulated	Measured	Simulated	Measured
0	100	100	10.33	-
7	89	98.2	10.33	-
20	74	83.6	10.32	16.09
100	37	55.3	10.31	15.26
500	11	32.9	10.30	15.44

Braverman et al. 2006 – 6 month study

The Braverman et al. (2006) study was conducted to determine whether prolonged exposure (6 months) to low levels of perchlorate (0.5, 1.0 or 3.0 mg/day) would perturb thyroid function. The study included a small number of individuals; however, iodine levels were comparable with those of the general population. The authors noted the limitations of the small sample size, but concluded that the results suggested that healthy, euthyroid individuals, with normal levels of iodine intake, can tolerate chronic exposure to perchlorate at doses of up to 3 mg/day (approximately 40 µg/kg/day) without any effects on thyroid function, including inhibition of iodine uptake.

The Braverman et al. study was simulated using the BBDR model, and predicted T3 and TSH levels were compared to the reported measurements. fT4 was not compared because it was not clear how to convert the T4 index to a concentration and vice versa. As with the Greer simulation, 90 ug/day was used for iodine intake. Baseline T3 and TSH are similar to the measured values. But, as was seen with fT4, the simulated change in hormone levels is severely dampened compared to the measured values.

Table 2. Simulation of Braverman et al. (2006) perchlorate study.

Dose	T3 (nM)		TSH (mIU/L)	
(ug/kg/d)	Simulated	Measured	Simulated	Measured
0	2.63	2.49	1.51	1.20
7	2.63	2.51	1.52	1.60
43	2.62	1.77	1.53	2.60

Téllez Téllez et al. 2005a, 2005b – Chile study in pregnant women

Téllez Téllez et al. (2005a, 2005b) reports the results of a longitudinal epidemiological study among pregnant women from three cities in Chile exposed to concentrations of perchlorate as high as 114

µg/L in the public drinking water. The focus of the study was to evaluate maternal thyroid function during pregnancy, neonatal thyroid function and developmental status at birth, and breast milk iodine and perchlorate levels during lactation. The National Academy of Sciences (2005) has reviewed this study in the context of health implications for perchlorate ingestion and concluded this study should be considered in the evaluation of the U.S. experience with perchlorate in drinking water. The total iodine nutrition among this cohort was also noted to be similar to that of U.S. pregnant women (Téllez Téllez et al. 2005a); therefore, this study should be a key consideration in evaluating the relationship between perchlorate exposure, changes in fT4 in pregnant women and developmental status.

Results from this study, relied upon for BBDR model parameters (specifically the elimination to urine parameter – CLFUP), indicated no effect on thyroid levels in early pregnancy, late pregnancy, or neonates at birth related to perchlorate in drinking water at concentrations up to 114 µg/L. It seems this study should provide a validation dataset for the impact of high concentrations of perchlorate exposure in drinking water on potential changes in fT4 or TSH.

The BBDR model was used to simulate the drinking water study. The predictions of fT4 are consistent with the negative results of the study, though the concentrations are again smaller than those observed. This is not a strong validation of the model given the weak trend of changes in hormone levels seen in comparisons to other studies.

Table 3. Simulation of the Tellez et al. study of pregnant women exposed to perchlorate via drinking water.

Dose	fT4 (pM)	
(ug/kg/d)	Simulated	Measured
0.01	9.74	12.5
0.08	9.73	12.2
2	9.69	12.7

Overall, the BBDR model reproduces the key elements of the findings from these three studies, which indicate that thyroid hormone levels are relatively insensitive to inhibition of thyroid iodine uptake by perchlorate concentrations several orders of magnitude higher than those predicted by the BBDR to affect fT4 in early pregnancy. In particular, it seems biologically implausible that concentrations of perchlorate up to 2 ug/kg/d were demonstrated to be without effect to pregnant women in the Tellez study, while the BBDR model predicts that perchlorate concentrations nearly an order of magnitude lower could result in changes in fT4 during the first trimester. During the first trimester, hCG increases the iodine uptake capacity of the thyroid and the T4 production rate so significantly that TSH concentrations are typically reduced. The BBDR model assumes that during the first trimester thyroid hormone production is controlled by both TSH and hCG but thyroid uptake is controlled by TSH only. However, hCG controls both organification and uptake. During pregnancy, hCG stimulates iodide transport and thyroid hormone synthesis through stimulation of the TSH receptor due to the structural similarity of hCG to TSH. This increase typically results in lower TSH levels (Pesce and Kopp 2014). Thus, during the first trimester, the thyroid is actually in a better position to respond to inhibition of iodine uptake through a direct TSH-mediated response if needed.

2. LINKING BBDR RESULTS TO NEURODEVELOPMENT OUTCOMES

Chapter 5 of USEPA (2017) focuses on the SAB's recommendation to "Identify literature and conduct analyses to support the model outputs for the downstream steps" from the BBDR's predicted changes in thyroid hormones following exposure to perchlorate. Specifically, Chapter 5 was developed to present the process USEPA used to identify literature to support the approach for derivation of the MCLG for perchlorate. USEPA (2017) states, "Based on the recommendations of previous peer review panels, USEPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes", and because of this assumption, a complete systematic review of the body of literature on this topic was not performed. Instead, a "focused review of the published literature" was conducted.

The approach is inconsistent with recent recommendations from the National Research Council regarding systematic review and evidence integration (NRC 2014). These recommendations are currently being incorporated into the USEPA's Integrated Risk Information System (IRIS) process and USEPA has recently released scoping and problem formulation materials for several new Integrated Risk Information System (IRIS) assessments, including ethylbenzene (USEPA 2014a), and naphthalene (USEPA 2014b). The approach applied in these assessments is intended to follow recommendations provided by the National Research Council (NRC 2013). While development of MCLGs are not part of the IRIS process, the application of systematic review principles in the identification of studies to define the relationship between fT4 and neurodevelopmental effects, is needed. The application of these principles will not only assist in defining the highest quality studies to address a specific research question, they provide a way to integrate all of the available evidence for the specific research questions raised by the SAB. Systematic reviews include the formulation of a specific question to be addressed and developing a protocol that specifies the methods that will be used to address the question. While a broad research question can lead to a large systematic review, if the research question is limited, such as in the case of perchlorate, then the systematic review becomes more focused.

For the USEPA (2017) MCLG approach, a systematic review question could have been easily developed based on the SAB recommendation (i.e. "Identify literature and conduct analyses to support the model outputs for the downstream steps") and the protocol would simply be focused on the methods for conducting the systematic review to address this very focused systematic review question in a transparent manner. Transparency being defined by USEPA as "sufficient information will be available to understand the scientific rational behind decisions, as well as, reproduce methods used to identify and evaluate data". However, in the case of the literature identified for consideration in the MCLG approach for perchlorate, a well-defined protocol for all steps of the process has not been developed and therefore is inconsistent with the recommendations of the NRC (2013):

> *"A priori decisions and a predefined protocol are critical during the systematic review process (Berlin and Colditz 1999; Dickersin 2002); the protocol should describe the following steps: the research question, the search strategy and data sources, the study inclusion and exclusion criteria, the data to be abstracted and derived from the original studies (such as sample size, exposure and outcome assessment methods, and confounders evaluated), the criteria and methods for pooling effect estimates and measures of variability among studies. Systematic reviews and meta-analyses need to be replicable; other investigators following the same steps should be able to identify the same articles, abstract the same data, and reach similar conclusions."*

At each step of the process for identifying studies for use in the development of the MCLG approach for perchlorate, a detailed set of criteria is needed. For example, if decisions are made to include or exclude any studies, there should be very detailed criteria indicating why studies were included or excluded and it should be specified prior to the initiation of the literature searching process. The criteria for each step should be described in such a way that an independent reviewer could use it to replicate the results of the literature search and review; however, there are several areas in the USEPA (2017) MCLG approach for perchlorate where this level of detail is lacking, making it difficult for an independent reviewer to replicate the results.

2.1 Systematic Review Research Questions

An overall hypothesis or systematic review research question should be developed that is based on the SAB recommendation to clarify the focus of the review and the linkage between altered maternal fT4 (as predicted by the BBDR model) and the potential for adverse neurodevelopmental effects in offspring. Some additional explanation as to how USEPA arrived at the specific neurodevelopmental outcomes of concern should be provided.

2.2 Searching the Published Literature

While the literature search key words are presented in the USEPA (2017) report, there is a lack of explanation as to the reasoning behind the focus on the outcome of concern. The research question should be used to develop the literature search. The major points used or considered in developing the literature search strategy should be presented. In addition, there should be a detailed explanation of the screening criteria used to screen the literature search results. Furthermore, USEPA (2017) does not report the details of the literature search results. For each search string reported in Table 9 of the USEPA (2017) report, a total number of citations identified should be reported. In addition, the criteria used to screen the original search results should be clearly reported in the document. Essentially, each step of the literature search and review should be reported in such a way that any independent party could easily reproduce the results reported in Chapter 5 of USEPA (2017). The lack of this type of information does not allow the reader to determine if any key studies may have been removed from consideration.

2.3 Literature Screening Approach and Selection of Key Studies

USEPA (2017) states that a 3 step approach was used to identify studies for consideration in the development of the approach for derivation of the MCLG for perchlorate. The approaches utilized by USEPA (2017) to identify the epidemiological studies for this evaluation were strictly focused on the appropriateness of the quantitative data for consideration in combination with the output of the BBDR model. Group 2 (studies with categorical analyses only) and Group 3 (studies with analyses not directly compatible with BBDR output) studies were apparently eliminated from consideration in the assessment. While not directly compatible with BBDR modeling output, it is possible that these studies may provide information important in understanding the potential relationship between changes in thyroid hormones and the potential for neurodevelopmental effects, as well as potential key confounders.

While 15 studies were identified in Group 1, only 5 of these were determined by USEPA to include analyses that could be used to connect the results of the BBDR model to incremental changes in adverse neurodevelopmental effects. A clearly defined set of inclusion and exclusion criteria should be developed to clearly convey to the reader why the other 40 studies in Groups 1, 2, and 3 were not considered. In addition, studies that provide no evidence of an inverse relationship between perchlorate exposure and serum thyroid function (e.g. Ghassabian et al. 2014; Modesto et al. 2015; Moleti et al. 2016; Noten et al. 2015) should also be considered to not only understand why these

results are in contrast to the potential research question, but also that the overall weight of evidence can be determined. It is possible that the majority of studies provide evidence that critical factors that are not reported in some of the available studies may explain the reported changes in serum thyroid function.

2.4 Assessment of Study Quality and Risk of Bias

According to recent recommendations from the National Research Council (NRC 2014), the National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT) method for the assessment of study quality and risk of bias of the literature (NTP 2015) is one method that should be considered for qualitative and quantitative assessments. "An assessment of study quality evaluates the extent to which the researchers conducted their research to the highest possible standards and how a study is reported. Risk of bias is related to the internal validity of a study and reflects study-design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect" (NRC 2014). Each study meeting inclusion criteria in Group 1, 2, and 3, should be evaluated against a predetermined set of study quality and risk of bias criteria and the results of this evaluation should be presented in the perchlorate MCLG approach report.

2.5 Uncertainties Critical to Characterizing Changes in Thyroid Hormone Levels in Pregnant Women Associated with Neurodevelopmental Changes in Offspring

The MCLG approach presented in USEPA (2017) to predict doses of perchlorate that would result in per unit changes in neurodevelopmental measures, is, as noted by USEPA (2017), "…dependent upon predictions from the BBDR model, the derivation of the distribution of fT4, and the evaluations of the relationship between fT4 and neurodevelopment. Each of these steps has inherent uncertainties associated with it."

A major source of uncertainty is related to the five studies in Group 1 with data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment (Pop et al. 1999, 2003; Finken et al. 2013; Korevaar et al. 2016; Vermiglio et al. 2004). None of these five studies relied upon data from US populations or have been demonstrated to have iodine intake similar to US populations. Yet according to Alexander et al. (2017) the reference range of both TSH and fT4 in pregnant women varies depending upon ethnicity. While two studies in Group 1 focused on population groups within the United States, neither were considered for the model because T4 and not fT4 was measured in the pregnant females (Oken et al. 2009) and the relationship between fT4 and neurodevelopment was evaluated in late pregnancy and did not reach statistical significance (Chevrier et al. 2011). USEPA (2017) (Section 6.5.1) states "there is no reason to believe that the impact of fT4 on neurodevelopment would differ by country, unless there is a substantial difference in iodine intake". While USEPA (2017) does make an effort to evaluate changes in iodine intake in women from various populations, including the US, there are not substantial data reported to validate the conclusions that the impact of fT4 on neurodevelopment would differ by population or uncertainty in iodine intake levels would have an impact on the derivation of the MCLG. This is inconsistent with data from the American Thyroid Association (Alexander et al. 2017) that suggest variability in the distribution of thyroid hormone levels across populations and even within ethnicities within a single population.

USEPA (2017) also notes that all five studies used for quantitative analysis relied on a one-time fT4 level during pregnancy (Section 6.5.5). The influence of changes in maternal fT4 on fetal brain development is likely greatest during early pregnancy. The variability in maternal fT4 levels during pregnancy and the lack of measurement of fT4 at time points throughout pregnancy in the studies relied upon introduces a significant amount of uncertainty to the assessment. As stated in USEPA (2017),

> *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see Figure 2) that operates around a "set-point." This set-point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance (Andersen, Pedersen, Bruun, & Laurberg, 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations (Andersen et al., 2002)."*

Several other areas of uncertainty are also highlighted by USEPA (2017). Specifically, USEPA (2017) noted that none of the five studies carried forward provided iodine intake levels (Section 6.5.3), which adds significant uncertainty to the estimates. Three of the 5 studies (Pop et al. 1999, 2003; Vermiglio et al. 2004) also have populations of less than 30 decreasing the statistical power of the studies (section 6.5.4) relied upon for establishing the relationship between changes in fT4 and neurodevelopmental changes. USEPA (2017) also noted uncertainties in regards to the analytical methods used to evaluate fT4 levels and while approaches are being introduced to standardize analytical methods, results at different time points and from different countries may vary considerably due to differences in analytical procedures (USEPA 2017). USEPA (2017) also notes that "there is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. This is exemplified by the fact that in this analysis larger unit changes are being seen with increasing percentiles of fT4 in most analyses." Finally, other confounders such as iron deficiency were not considered in the analysis. Iron deficiency in pregnant mothers may also be associated with hypothyroxinemia (Yu et al., 2015) and failing to directly account for a relationship between iron deficiency and hypothyroxinemia may introduce an uncertainty into this analysis.

While all of these uncertainties are noted by USEPA (2017), there is no attempt to adjust the MCLG approach in any way to account for these uncertainties. Many of these, especially confounders such as iron deficiency in the study population and a lack of information on iodide intake, can have a significant effect in characterizing changes in thyroid hormone levels associated with changes in neurodevelopmental outcomes. In the absence of adequately accounting for these uncertainties, it is difficult to conclude that small changes in a specific thyroid hormone (e.g. fT4) may accurately predict the potential for neurodevelopmental effects.

3. COMPARISON TO PREVIOUS ASSESSMENTS

In the MCLG approach, USEPA (2017) has focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time) based on the measurement of fT4 during early pregnancy. Results from previous studies have provided the basis for No Observed Effect Levels (NOELs) for health effects of perchlorate in the development of Reference Doses and currently recommended Health Reference Levels (HRLs), including Greer et al. (2002) which reported results similar to the BBDR model in human test subjects. Results reported by Greer et al. (2002) in which subjects were exposed to perchlorate in drinking water at doses of 0.007, 0.02, 0.1, or 0.5 mg/kg/day for 14 days demonstrated a NOEL for perchlorate inhibition of radioiodide uptake by the thyroid NIS following exposure to 7 µg/kg/day. The point of departure from the Greer et al. (2002) study represents a perchlorate level that precedes the inhibition of iodine uptake by the thyroid. The NAS RfD developed based on the point of departure (POD) from this study is a departure from the Agency's traditional approach of using a No Observed Adverse Effect Level (NOAEL) for regulatory actions. The NAS's use of a No Observed Effect Level (NOEL) is based on "using a nonadverse effect that is upstream of the adverse effect [which] is a more conservative and health protective approach".

While these studies have not been conducted in pregnant women (the population of interest for the MCLG approach), as noted by in USEPA (2017):

> *"…the BBDR model predicts very little difference in non-pregnant and first-trimester response to perchlorate. This likely occurs because the half-life of (organified) iodine in the adult thyroid is around six months, hence the availability of thyroidal iodine in the first trimester pregnant woman is determined to a very large extent by her nutrition and perchlorate exposure several years preceding pregnancy."*

This suggests comparison of the current modeling results to those from studies conducted in adults should provide insight into the predictions of the model and the conclusions regarding the changes in thyroid hormone levels that may result in neurodevelopmental effects.

The current approach for deriving the MCLG assumes any exposure to perchlorate reduces fT4 to some extent (p. 3-17 of USEPA doc). In addition, linear regression analyses conducted to evaluate the relationship between changes in fT4 and neurodevelopmental effects further assumes any change in fT4 results in some risk of neurodevelopmental effects. These assumptions are in contrast to the results from the Greer et al. (2002) in which exposures to perchlorate were as high as 500 µg/kg/day and no impact on thyroid hormone levels was observed. This was true for both men and women. In addition, in a study conducted by Braverman et al. (2006), 6 months of exposure to perchlorate in capsules at doses up to 3 mg/day (approximately 40 µg/kg/day) was reported to have no effect on thyroid function, including inhibition of thyroid iodide uptake as well as serum levels of thyroid hormones, TSH, and Tg in a small group of volunteers.

USEPA (2017) notes (p. 6-16) that from results of the literature review, it appears the relationship between maternal fT4 and fetal brain development has a temporal relationship, with this influence likely being greatest in early pregnancy (i.e. prior to mid-gestation). The focus of the evaluation is on gestational weeks 12, 13, and 16, where the mother's fT4 levels will have the greatest impact on the fetus. This should allow for comparison to the model results in pregnant women to results from previous studies focused on identification of perchlorate concentrations that would impact fT4 levels in adult women, such as the Greer et al. (2002) study.

In comparing the current BBDR model predictions to previous assessments, in Tables 35 and 40 of USEPA (2017) a perchlorate dose of 0.3-0.4 µg/kg/day would result in a 1% increase in the

proportion of the population with hypothyroxinemia and a perchlorate dose of 2.1-2.2 µg/kg/day would result in a 5% increase in proportion of the population with hypothyroxinemia. These modeling results suggest a potential for a significant change in thyroid hormones, as well as adverse effects on neurodevelopment at doses of perchlorate exposure for which there is evidence that decreases in fT4 are not observed. Based on the mode of action proposed by USEPA (2017), decreases in fT4 and increases in TSH would be prerequisite steps for the potential for neurodevelopmental effects. These changes in hormone levels are not observed in workers in the Greer et al. study following exposure up to 500 µg/kg/day. The current assessment suggests population changes in fT4 would be observed that would shift the proportion of pregnant women that would be hypothyroxinemic at doses of perchlorate below the previously defined NOEL (7 µg/kg/day).

Table 39 of USEPA (2017) provides the predicted dose of perchlorate per unit change in neurodevelopmental measure for low iodine intake individuals. Considering multiple neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time), those for IQ are approximately at or above (6.5 – 45 µg/kg/day) the NOEL from Greer et al. (2002) and are associated with decreases in fT4 of 4.3 to 18.7%. The remaining doses associated with the other neurodevelopmental endpoints are 1.7 to 3.0 µg/kg/day and associated with decreases in fT4 of 1.3 to 2.4%. These percent changes in fT4 are very small and considering the potential uncertainty and variability in measuring fT4 levels, may not be detectable in the clinical setting. The dose of perchlorate estimated to result in a 1% or 5% increase in the proportion of hypothyroxinemic pregnant women is even lower, ranging from 0.3 to 2.2 µg/kg/day. Multiple studies in adults and pregnant women (Greer et al. 2002; Braverman et al. 2006; Téllez Téllez et al. 2005) provide evidence that no impact on iodine uptake or thyroid hormone levels would be expected at these dose levels. Based on the mode of action proposed by USEPA (2017), these events would be precursors necessary for the development of neurodevelopmental effects.

4. OVERALL CONCLUSIONS/COMMENTS

- While we applaud the EPA for the application of a BBDR model in the MCLG approach, as these models integrate the available science for a compound of interest, there is some concern that uncertainties inherent in the model call into question its proposed application in the risk assessment for perchlorate and whether it is fit for that purpose. While the hormone component of the model is a definite scientific improvement in terms of incorporating the available biology, there is a lack of data to provide validation of multiple steps in the proposed approach and of the assumptions/parameters within the BBDR model.
- Many of the changes in fT4 that are predicted by the MCLG approach to impact the population distribution of fT4 and therefore result in per unit changes in neurodevelopmental outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to suggest that the extended version of the BBDR model has a capability to estimate small changes in fT4 with precision that is not demonstrated by any adequate validation. Further, the model predictions of fT4 underpredict observed data in various clinical studies by substantially more than 1.3-4.3%. This suggests that the model is not precise enough to predict such small changes in fT4. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as to whether these slight changes could be measured clinically, considering the greater impact of iodine intake on hormone levels.
- Until additional data are available to validate current extensions of the BBDR model to the pregnant woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake and, therefore, impacts on fT4. Based on recommendations from the National Research Council (2005), points of departure provided by these studies used in combination with uncertainty factors were considered to be protective of sensitive subpopulations, and provides a basis for future risk management decisions.

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Post-Meeting Peer Review Summary Report

External Peer Review for EPA's *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*

March 17, 2017

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EXECUTIVE SUMMARY

Versar, Inc. (Versar), a contractor for the U.S. Environmental Protection Agency (EPA), coordinated an external peer review of EPA's draft Biologically Based Dose-Response (BBDR) Model for perchlorate in drinking water and an accompanying draft model report. The draft model report is entitled "Biologically Based Dose-Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses," and was authored by EPA in collaboration with the Food and Drug Administration (FDA). As part of the peer review of the BBDR model and model report, Versar organized a two-day public peer review meeting in Arlington, Virginia on January 10-11, 2017. The peer review was initiated with a pre-meeting written peer review managed by Versar and conducted by eight independent expert peer reviewers. The role of the peer reviewers was to evaluate the scientific and technical merit of the draft BBDR model and model report and provide their responses to seven charge questions. Peer reviewers were responsible only for evaluating the quality of the science included in EPA's BBDR model and model report, and were not asked to make any regulatory recommendations or to reach consensus in either their deliberations or written comments. The two-day peer review meeting, which directly followed the written peer review period, was held to discuss the scientific basis supporting EPA's BBDR model and model report and to provide members of the public with an opportunity to present oral comments and observe the peer reviewer deliberations.

On the first day of the meeting, Versar began by providing information on the overall peer review process and introducing the peer reviewers. Following a welcome by EPA, authors from EPA and FDA provided background information on the draft BBDR model and model report. Next, an observer comment session was held, after which the peer reviewers began their discussions. The discussion was moderated by the Chair, Dr. Hugh Barton, and focused on individual responses to EPA's charge questions. The second day of the meeting began with brief remarks from Versar and EPA and then continued with discussion of responses to the charge questions.

Following the meeting, peer reviewers were given additional time to complete their individual written reviews, which were submitted to Versar upon completion. These final written comments (contained in Sections III, IV, V, VI, VII of this report) fall into three categories: general impressions, responses to charge questions, and specific observations. Written peer review comments, as well as comments submitted to the docket by members of the public, will be considered by EPA as it revises the BBDR model and model report.

Important discussion points at the meeting, developed by Dr. Barton with assistance from the entire peer review panel, are summarized below by charge question.

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General Comments

In response to a 2013 report from EPA's Science Advisory Board (SAB) Perchlorate Advisory Panel (U.S. EPA, 2013[1]), EPA undertook the development of biologically based dose-response models for the effect of perchlorate on thyroid hormones in women and their offspring during end of term pregnancy and lactation, which are the subject of the current peer review. The model represents a major effort to utilize quantitative computational modeling to capture available scientific information describing perchlorate inhibition of the sodium iodide symporter (NIS) and the relationships between iodine intake and circulating levels of thyroid hormones including T4 and T3. Thyroid hormones, in turn, are major determinants of neurodevelopment during pregnancy, infancy, and childhood. Notable strengths of this effort are that it is based upon the consensus mode of action (MOA) for perchlorate inhibition of iodine uptake, uses human iodine and perchlorate toxicokinetic data, addresses sensitive life stages, and is designed to be protective of serious, unambiguous adverse health effects known to occur in humans (i.e., neurodevelopmental deficits) associated with thyroid hormone deficiencies.

- The peer reviewers identified a number of areas for improvement or modification of the existing models, as noted in this executive summary and in the individual comments, with respect to modeling earlier pregnancy, the limited hypothyroxinemic range, and additional literature. It is recommended that the Agency scientists and regulators develop a plan for further actions in order to maximize the benefit of any model revisions that are undertaken and to make decisions about priorities, timelines, and resources. Models can always be improved, but the goal is to have a model that is fit for the intended purpose; the lack of a clear definition of that purpose for this model (i.e., how the model outputs would be used in developing the desired drinking water regulations) contributed to the difficulty the peer reviewers had in assessing whether the model was sufficiently good to apply.

- Changes in thyroid hormones (a model output) represent precursor events and are indicators of the processes that lead to neurodevelopmental outcomes. The vision of SAB Perchlorate Advisory Panel (U.S. EPA, 2013) was that modeling would facilitate linkage between several critical steps: perchlorate exposure and alterations in iodine handling, iodine status and impacts on thyroid hormone levels, and finally, the relationship between thyroid hormone status and neurodevelopment in critical fetal and post-natal periods. Recent studies cited by individual peer reviewers for endpoints such as IQ, provide information for this final linkage. Planning how model predictions of perchlorate-mediated changes in thyroid hormones would be used should clarify what efforts to undertake in model revision and ensure any further model development is fit for purpose.

- As further modeling efforts are undertaken, it is recommended that the Agency establish a collaborative interaction with clinicians and epidemiologists with expertise in thyroid function and neurodevelopment. This would assist the modelers by insuring access to

[1] U.S. EPA. 2013. SAB advice on approaches to derive a maximum contaminant level goal for perchlorate, U.S. Environmental Protection Agency, Science Advisory Board, EPA/ SAB/13/004. Available at: https://www.epa.gov/dwstandardsregulations/perchlorate.

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and awareness of published literature that could be useful in the modeling, helping make decisions around interpretation or usage of existing literature, and maximizing the biological and clinical credibility of the modeling effort.

- The current report was challenging for the multidisciplinary group of peer reviewers to understand and evaluate. It is recommended that future documents strive to clearly convey the scope of the modeling effort, the biology the model addresses, and the model applications. The report should be written for a broad audience including regulators and scientists with expertise in risk assessment, modeling, clinical thyroid hormone status and neurodevelopment; this re-emphasizes recommendations of the SAB Perchlorate Advisory Panel (U.S. EPA, 2013). The complexity of the modeling effort makes clear communication and documentation challenging, but it is essential for moving forward this state-of-the-art method in deriving standards for perchlorate protective of human health in these critical life stages. The report needs to clearly state the case for why the current model, which likely could always be improved given additional time and resources, represents a fit-for-purpose solution applicable to current efforts to develop regulatory standards for perchlorate.

Question 1A. Model structure

The modeling structures reviewed address end of term pregnancy (gestation week 40) and formula-fed and nursing infants and their mothers. The models incorporate submodels for perchlorate pharmacokinetics and its interaction with NIS in multiple tissues and kinetics for iodine, T3, and T4 (both total and free T4). This represents a major augmentation of the earlier models that were limited to perchlorate kinetics and impacts on NIS as measured by radioiodide uptake inhibition (RAUI). The report was confusing to the peer reviewers in its coverage of the lactation/formula feeding model and the previously published end of term model.

- Iodine intake and production of thyroid hormones are critical for neurodevelopment throughout pregnancy and after birth, so it was a concern of the peer reviewers that the modeling addressed end of term pregnancy and the post-natal period, but not earlier in pregnancy. The peer reviewers recommend modeling for maternal iodide and hormone levels earlier in pregnancy. Available literature should support analyses and modeling for pregnancy including literature on maternal perchlorate, iodine, and thyroid hormone status, notably in the first half of pregnancy and to some degree throughout pregnancy. Revising the model to include the first-trimester pregnancy would allow for model evaluation against large epidemiological data sets in which drinking water perchlorate estimates are reported. This work would focus on maternal iodide and thyroid hormone as drivers for the effects in the fetal brain and neurodevelopment.

- Feedback regulation between TSH and T4 is not currently incorporated in the model structure consistent with a focus on isolated hypothyroxinemia (low free T4 and normal TSH in blood). While the peer reviewers agreed that inclusion of TSH feedback processes would be ideal, there were different perspectives on the necessity of this effort for EPA's needs. Several reviewers felt inclusion of the TSH feedback would help demonstrate that the model reflects the known biology and measures that clinicians rely

on. Further, the peer reviewers reviewed the Silva and Silva (1981)[2] paper, which used by EPA to support that there was a wide range of iodine intakes over which T4 decreased but TSH remained relatively constant, and determined that it was likely that the assays used at that time would be of such limited sensitivity to make the conclusions highly uncertain. Others felt that the model as constructed is a fit-for-purpose representation that would assist EPA in addressing implications of the lower end of the dose-response for perchlorate; this model would not be appropriate to apply for greater exposures that could initiate compensatory mechanisms that may buffer the effect of perchlorate on thyroid iodide uptake or, alternatively, might create conditions better characterized as hypothyroidism (low free T4 and elevated TSH).

- NIS inhibition by co-exposure to other inhibitors in diet or the environment is known, but was not considered essential to explicitly incorporate in the modeling at this time. This likely contributes to the variability in the observed human data to which the modeling is being compared. Limitations in data, and perchlorate being a substantially more potent NIS inhibitor than several other compounds, supported the current formulation of the model, though extension in the future would be useful.

Question 1B. Model parameterization

Model parameters and their values were described in the report text and tables, and indicating the literature supporting the parameter or by calibration with data.

- The model parameterization largely appears well described and consistent with the scientific information used in model development, though concerns were noted by some peer reviewers about the calibration as discussed below in response to Charge Question 3. Individual reviewers noted some parameters between the term pregnant model and the lactation model that were perhaps not entirely consistent. Also important would be the consideration of serum thyroid autoantibody status in the derivation of serum thyroid hormone parameters used for model calibration. A peer reviewer suggested reviewing and revising as appropriate the description of fT4 metabolism to fT3 and rT3 including life stage dependencies.

- Reviewers noted that are references published prior to or since the model development and reporting process which provide additional data for model calibration or evaluation. Since the process of model revision and reporting will inevitably take an extended period (e.g., fraction or multiple of years), clearly describing when the literature search was undertaken, and potentially repeating the search to identify new references that have not been accounted for in the modeling, would help future reviewers given the explosion of publications in recent years on thyroid hormones and neurodevelopment as well as perchlorate exposure.

[2] Silva, JE; Silva, S. 1981. Interrelationships among serum thyroxine, triiodothyronine, reverse triiodothyronine, and thyroid-stimulating hormone in iodine-deficient pregnant women and their offspring: effects of iodine supplementation. J Clin Endocrinol Metab 52: 671-677.

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Question 1C. Fetal thyroid hormone modeling

The peer reviewers agreed that modeling maternal thyroid hormones would be a sound basis for evaluating the potential for fetal effects. Clinical studies have related maternal thyroid hormone levels during pregnancy to neurodevelopmental outcomes such as IQ, brain imaging, or diagnoses such as ADHD. While these neurodevelopmental changes are largely due to changes in the fetal brain and it would be ideal to model fetal thyroid hormone status for which some data exist in literature during later pregnancy when fetal production contributes, there would not be direct data relating fetal hormone levels with developmental outcomes. Thus, the priority would be to capture maternal hormone status during pregnancy over modeling the fetus.

Question 2. Modifications to existing models

Two parameters with significant impact on predictions for perchlorate were modified. KM_TPNG characterizes the strength of perchlorate-mediated inhibition of iodine transport by the sodium-iodine symporter (NIS). VMAXC_MKP describes the maximal rate of perchlorate transfer to breast milk.

- The refitting of *in vitro* data to obtain the KM_TPNG and use of that value to predict the Greer et al. (2002)[3] data was well described in the report and a previous publication (Schlosser 2016[4]) and is scientifically supported. A few peer reviewers felt the data could be used to characterize a range of values consistent with the data to then use in characterizing the uncertainty in the model predictions.

- The change in the VMAXC_MKP was not as readily understood from the report, but following the presentations by the model authors, the use of the newer data set to re-estimate the value appeared scientifically supported. Again, some panel members felt it would be valuable to characterize a range of values consistent with this data that could be used in characterizing uncertainty in the model predictions.

Question 3A. Model calibration and sensitivity analysis

The model calibration was described in the text and tables of parameters. This is a large and complex model with parameters supported or estimated using varied *in vitro* and *in vivo* data sets making the calibration effort, evaluation of the models ability to capture the data, and its review a complex task.

- It is challenging to assess how constrained are the parameter values by the available data, what range of values might also be reasonably consistent, and how much variation in model outputs might result from alternative parameterizations. The peer reviewers had a range of opinions on the calibration approach described in the report (fitting individual parameters and varying iodine intakes to try to visually capture the range of observed

[3] Greer, MA; Goodman, G; Pleus, RC; Greer, SE. 2002. Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect 110: 927-937. http://dx.doi.org/10.1289/ehp.02110927

[4] Schlosser, PM. 2016. Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter (NIS) based on in-vitro and human in-vivo data. J. Appl. Toxicol. 36(12): 1531–1535. *doi:* 10.1002/jat.3337

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data) and alternatives such as application of statistical methods to characterize the deviations between model predictions and data. These perspectives reflect the value of statistical methods tempered by the challenges of applying them with complex models and data sets with varied measurements (e.g., urinary iodine, plasma thyroid hormone, breast milk perchlorate). Several peer reviewers felt that the current model calibration was good quality given the available data, while at least one peer reviewer felt a more statistical approach was essential along with a focus on explicitly characterizing the uncertainty in model outputs given the uncertainties of input parameters.

- A challenge for characterizing the calibration is that the model effectively represents an individual (a mother and her fetus at term, a formula-fed infant, or a mother and her nursing infant). By contrast, the available data are for populations with substantial biologic and environmental variability, including large variations in iodine levels in formula, and uncertainty about the extent to which infants received some combination of formula and their mother's milk. It was noted that even in regions where iodine intake is substantially below levels considered adequate, only a relatively small fraction of women and/or their infants fall into the lowest percentiles of fT4 or other measures of thyroid function. Thus, a model that predicts low thyroid hormone levels with low iodine intake reflects a specific portion of the population. Creating a reasonably behaved model of the individual is generally an essential first step toward a population model. The use of data reflecting the population variability to calibrate an individual model by varying select parameters (iodine intake in this report) can make the results appear less predictive than if one were fitting data collected from a well-controlled preclinical or clinical study. As noted in Charge Question 1, scoping out the use of the model in applications for developing drinking water regulations would be beneficial for making a determination that the current model, or a somewhat modified version of it, is fit for current purposes.

Question 3B. Sensitivity analysis

Local sensitivity analysis was conducted for total and fT4 (with fT4 shown in the main text) for formula- and breast-fed infants and the nursing mothers under selected iodine intake conditions to assess which parameters were particularly important for determining predicted hormone status. This analysis reflected the role of fT4 as a precursor predicted by the model that could be associated with neurodevelopment.

- The sensitivity analysis presented was valuable, but more limited than desirable. Some on the peer reviewers recommended presenting at least a qualitative evaluation of how well supported by available data were the important model parameters, as identified by the sensitivity analysis. Evaluating the impact on model predictions of the range of values consistent with the data for the most sensitive parameters could inform the evaluation of the accuracy of model predictions and the utility of further efforts to improve calibration.

- Local sensitivity analyses using the model outputs used to compare to data (e.g., urinary or milk iodine or perchlorate as well as serum thyroid hormone levels) under the appropriate conditions to simulate the study from which the data was obtained is a way

to identify which parameters these data are sensitive to and thus, which parameters the data actually inform.

Question 3C. Level of precision

- As noted in Charge Question 1, it is difficult to assess whether the model is fit for purpose, absent a description of how the model would be applied. Some reviewers felt statistical comparisons of model predictions and empirical observations would inform the assessment of precision and model adequacy.

Question 4A. Hypothyroxinemia reference ranges

- Given the model is characterizing iodine and thyroid hormone concentrations under conditions of isolated hypothyroxinemia (i.e., decreased free T4 with unchanged TSH), it is necessary to identify when the model can and cannot be considered applicable. While some concerns were expressed about the limited data used, the characterization of the reference ranges and the normalization procedures used was generally considered reasonable for purposes of identifying when conditions would make the model too uncertain to apply (e.g., hypothyroidism).

- Peer reviewers with the greatest expertise in clinical thyroid function indicated that isolated hypothyroxinemia is only defined and applied clinically during pregnancy. This means defining ranges of model applicability as described in the previous bullet cannot readily be informed by clinical practice.

- Peer reviewers expressed concerns and a range of views about the potential use of the reference ranges for assessing health effects in contrast to defining regions of model applicability. Correlations of effects, as well as the degree of effects on neurodevelopment, generally are greater as one moves to lower percentiles in the distribution of fT4 levels. This raises greater concerns about predictions in the lower fT4 range. Capturing this apparently continuous exposure-response relationship rather than treating it as if no effect occurred until one reached a defined low level was considered appropriate by several peer reviewers.

Question 4B. Model predictions for zero intake of perchlorate

- The ability of the model to predict iodine and thyroid hormone levels in the absence of perchlorate is an important consideration. This was challenging to assess due to a number of factors, including report presentation. Assessing model performance by looking at the y-axis (no perchlorate) of the dose-response graphs is difficult; presenting this aspect of the model perhaps as specific tables would facilitate this evaluation. Most people with low iodine intake are still euthyroid, so modeling predicting reduced thyroid hormones with low iodine appears to address a sensitive group within the overall population. There are sources of variability in the data for people without apparent perchlorate exposure not directly addressed in the modeling, including exposure to other NIS inhibitors, as noted above and in the report itself.

Question 4C. Lactating mother

- The peer reviewers agreed that the concern for the lactating mother was a concern that her nursing infant would obtain sufficient iodine and hormones in the mother's milk to maintain levels necessary for optimal neurodevelopment. The model may need to track maternal thyroid hormone levels to appropriately address maternal iodine balance and distribution of maternal hormones into breast milk, but the hormone levels are not strongly related to maternal health endpoints and should not be a focus of analyses.

Question 5. Robustness of model predictions and sensitivity at lower perchlorate dose levels

- The peer reviewers generally agreed that for all life stages the model predictions were likely to be more robust with higher iodine intake and no or low perchlorate (i.e., minimal perturbation from euthyroid conditions). Thus, as perchlorate concentration becomes higher, there is likely to be more substantial iodine inhibition and greater perturbation of thyroid hormone levels. As iodine intake gets lower, the model predictions become substantially more uncertain. This is notably true because the model does not include TSH feedback regulatory processes and as characterized by the model developers is inappropriate for predicting thyroid hormone levels under conditions of hypothyroidism.

Question 6. Empirical functions to predict thyroid hormone levels

- Inclusion of empirical functions or factors in this model to adequately simulate the data to which the model is being compared appears necessary and reasonable. Whether this arises because the model structure is not quite consistent with biological processes or because there are unrecognized biology involved is uncertain. Not including the empirical functions would increase discrepancies with available data making the model predictions less desirable.

Question 7. Characterization of model predictions

- The models represent a major and important effort to quantitatively characterize the biological relationships between iodine and thyroid hormones (T3 and T4) and predict the potential for perchlorate impacts on NIS resulting in perturbations in iodine and thyroid hormone levels that could be associated with alterations in neurodevelopment. Reviewers had a range of opinions on the model's predictive capabilities reflecting their different perspectives on the current model structure and its calibration. As noted in the discussion of calibration, this is essentially a model of individuals with potentially varying iodine intake rather than a population model. A model that well predicts the full range of population behaviors, while desirable, would need to be a follow-on effort based upon a model such as this that reasonably captures the biological processes and relationships occurring in an individual. The robustness of the predictions is not a fixed property of the model, but also reflects the application of the model and results, thus determining whether the model and its predictions are fit-for-purpose. The growing literature on the relationship between iodine status, thyroid hormone status, thyroid

autoantibody status, and neurodevelopment in pregnancy, notably early gestation, presents opportunities to more fully capture effects on neurodevelopmental outcomes of policy interest such as IQ.

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I. INTRODUCTION

Background on Draft BBDR Model and Model Report

Perchlorate is a naturally occurring and manufactured chemical anion that consists of one chlorine atom bonded to four oxygen atoms (ClO4-). Perchlorate is commonly used as an oxidizer in rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. It is naturally occurring in some fertilizers. On February 11, 2011, U.S. Environmental Protection Agency (EPA) determined that perchlorate meets the Safe Drinking Water Act (SDWA) criteria for regulation as a contaminant and is developing a National Primary Drinking Water Regulation (NPDWR) for perchlorate in accordance with the requirements under the SDWA. EPA has collaborated with Food and Drug Administration (FDA) scientists to implement the EPA Science Advisory Board (SAB) Perchlorate Advisory Panel recommendations (U.S. EPA, 2013) to develop a Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) or Biologically Based Dose Response (BBDR) model that will integrate available health related information in a robust and transparent analysis of the effects of perchlorate on thyroid hormone production. The draft model predicts changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels. The model integrates previous perchlorate and iodine models for thyroid hormones in formula-fed and nursing infants, as well as lactating women. The model predicts the effects of perchlorate on serum thyroid hormone concentrations in infants exposed via ingestion of formula mixed with contaminated drinking water or breast milk. EPA is considering deriving a perchlorate maximum contaminant level goal (MCLG) by linking BBDR model output to information from literature to account for adverse health outcomes.

Peer Review Process

On March 1, 2016, EPA announced in the Federal Register (81 FR 10617) a request for nominations for peer reviewers for EPA's Biologically Based Dose-Response (BBDR) model for perchlorate in drinking water and the supporting draft model report. Consistent with guidelines for the peer review of highly influential scientific assessments (HISA), Versar, Inc., an EPA contractor, was tasked with assembling eight scientific experts to evaluate the BBDR model and model report.

The peer review selection process was initiated with a four-week public nomination period that was held from March 1 to 31, 2016, as documented in the Federal Register (81 FR 10617). During this period, members of the public were able to nominate scientific experts with knowledge and experience in one or more of the following four areas: (1) PBPK, PBPK/PD and/or BBDR modeling, (2) fetal and neonatal thyroid endocrinology (clinical and experimental), (3) iodide homeostasis, and (4) perchlorate toxicology and mode of action or adverse outcome pathway. Concurrently, Versar conducted an independent search for qualified scientific experts to augment the list of publically-nominated candidates.

On June 3, 2016, EPA announced in the Federal Register (81 FR 35760) that they expanded the scope of the peer review published in the March 1, 2016 Federal Register to include the review of the application of the BBDR model to develop a perchlorate MCLG. With this change in scope, the Federal Register requested additional nominations for peer reviewers with knowledge

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and experience in a fifth area: human health risk assessment with an understanding of thyroid function (preferably in the sensitive life stages of interest), the importance of maternal thyroid hormone homeostasis in each stage of gestation, hypothyroxinemia, neurodevelopmental assessment indices for young children including the Bayley's Scale, the toxicity of perchlorate, epidemiological assessment techniques, and statistics. A four-week public nomination period was held from June 3 to July 5, 2016. Persons nominated during the March 1, 2016 nomination period did not need to be re-nominated under this June 3, 2016 notice and were considered for selection for the interim and final list of peer reviewers. Concurrently, Versar conducted an independent search for additional qualified scientific experts to augment the list of publically-nominated candidates.

On September 30, 2016, EPA announced in the Federal Register (81 FR 67347) that they will have separate peer reviews for the BBDR model and model report (Panel 1) and the methods for applying the model to inform development of a perchlorate MCLG (Panel 2), to allow the Agency to consider peer reviewer comments on the model prior to developing the MCLG. All experts identified in both nomination periods were considered for Panel 1 (BBDR model and model report). All together, Versar contacted 52 experts (20 publicly-nominated, 32 Versar-identified). Of these, 27 were both interested and available, including 11 nominated by the public and 16 identified by Versar.

Versar considered and screened all 27 candidates against the selection criteria described in both the Federal Register Notices dated March 1, 2016 and June 3, 2016, which included: (1) having demonstrated expertise in the areas described above, based on information in their submitted resume, biographical sketch and/or current publications, (2) being free of any conflict of interest (COI), and (3) being available to participate in-person in a one- or two-day peer review meeting in the Washington DC area. Candidates were queried on multiple occasions on their availability, with the most recent query requesting availability for a January 2017 meeting on the BBDR model and model report.

Following the completion of the screening process, Versar narrowed the list of potential reviewers to 19 candidates and the names, professional affiliations, expertise, education, and professional experience of these candidates were included on an interim list which was published in the Federal Register on September 30, 2016 (81 FR 67347). The Federal Register provided a 21-day period for the public to submit relevant information or documentation on the proposed list of candidates that Versar should consider during the evaluation process of selecting the final reviewers. One set of public comments was received on the interim list of potential reviewers.

On October 27, 2016, following the close of the public comment period on the proposed list of reviewers, Versar selected the eight experts for who, collectively, provide expertise spanning the multiple subject matter areas covered in the BBDR model and model document and, to the extent feasible, best provide a balance of perspectives. Biographical sketches for each of the selected reviewers are included in Appendix A.

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PEER REVIEWERS

Hugh A. Barton, Ph.D.
Pfizer, Inc.

Michael H. Lumpkin, Ph.D., DABT
Center for Toxicology and Environmental Health, LLC.

Claude Emond, Ph.D.
University of Montreal

Elizabeth N. Pearce, M.D., M.Sc.
Boston Medical Center/Boston University School of Medicine

Dale Hattis, Ph.D.
George Perkins Marsh Institute, Clark University

Stephen M. Roberts, Ph.D.
University of Florida

Angela M. Leung, M.D., M.Sc.
UCLA David Geffen School of Medicine

Joanne F. Rovet, Ph.D.
The Hospital for Sick Children (Toronto)

Peer Review Meeting

On January 10 and 11, 2017, Versar convened a public peer review meeting in Arlington, Virginia. This meeting was held to discuss the scientific basis supporting EPA's draft Biologically Based Dose-Response (BBDR) Model for perchlorate in drinking water and an accompanying draft Model Report and to provide members of the public with an opportunity to observe the peer reviewer deliberations. The meeting followed the public comment period on the draft BBDR model and model report and the pre-meeting written peer review period, during which the eight selected peer reviewers evaluated EPA's draft BBDR model and model report and provided preliminary comments in response to the seven charge questions.

Versar managed the pre-meeting registration period, which allowed members of the public to register to attend the meeting in person or remotely via teleconference and/or webinar. Members of the public were able to register by telephone, email, or facsimile. In advance of the meeting, Versar provided all registered attendees with pre-meeting handouts, which included the agenda (Appendix B) and logistics information. Approximately 35 public observers attended the peer review meeting in person and 31 observers attended the meeting via teleconference and/or webinar. A list of pre-registered meeting attendees is provided in Appendix C.

Peer Review Meeting – Day One

On the first day of the meeting, Versar began by providing information on the overall peer review process and introducing the peer reviewers. EPA's introduction to the meeting was made by Mr. Eric Burneson, the Director of Standards and Risk Management Division. In addition, the model authors, Dr. Jeff Fisher from FDA and Dr. Paul Schlosser from EPA gave technical presentations model development, as well as context, results and focus of the model. Opportunity for peer reviewer questions followed each presentation. A brief observer comment session followed these technical presentations, during which two individuals presented oral comments: Kevin M. Morley of American Water Works Association and Richard Pleus of Intertox, Inc. Following the observer comment period, the peer reviewers began their

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discussions on the BBDR model and model report, which centered on individual responses to EPA's first three charge questions. The discussion was moderated by the Chair, Dr. Hugh Barton.

Peer Review Meeting – Day Two

The second day of the meeting began with brief opening remarks from Versar, followed by a welcome from Dr. Peter Grevatt, the Director of EPA's Office of Ground Water and Drinking Water. The peer reviewers then continued their discussion of the charge questions, beginning where they had left off on Day One (Charge Question 4).

Preparation of Post-Meeting Comments

Following the public peer review meeting, peer reviewers were given additional time to revise and complete their individual pre-meeting written reviews. These final written comments are contained in Sections III, IV, V, VI, VII of this report. Written peer review comments, as well as comments submitted to the EPA docket by members of the public, will be considered by EPA as it revises the BBDR model and model report.

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II. CHARGE TO REVIEWERS

The U.S. EPA's Office of Water is in the process of developing National Primary Drinking Water Regulations for perchlorate under the Safe Drinking Water Act. In 2012, EPA submitted a white paper *Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate* (U.S. EPA, 2012) to the Science Advisory Board (SAB) for review. The white paper presented scientific information published since the National Research Council (NRC) released their 2005 Report "Health Implications of Perchlorate Ingestion" and described how EPA derived a range of Maximum Contaminant Level Goal (MCLG) values for life stages of concern. In their 2013 report, the SAB concluded that EPA should: 1) consider exposure to the following sensitive life stages: the fetuses of hypothyroxinemic pregnant women and infants exposed to perchlorate through either water-based formula or the breast milk of lactating women, and 2) derive the MCLG using a physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model to account for exposure differences and biological differences across life stages, including sensitive life stages. Specifically, the SAB found that the 'default algebraic approach provides limited ability to address the various exposure and biological factors affecting sensitivity to perchlorate at different life stages.' The SAB concluded that from a scientific standpoint it would be more appropriate to base the MCLG derivation on the perchlorate mode of action, using PBPK/PD modeling to relate perchlorate concentrations in drinking water to biological effects rather than the default approach.

The SAB report referenced a report by Lumen et al. (2013) on the effect of perchlorate on thyroid hormone perturbations for pregnant mothers and fetuses, as well as their work to extend a physiologically-based pharmacokinetic/pharmacodynamic iodine uptake inhibition (PBPK/PD-IUI) model with links to serum thyroid hormone levels, as a starting point for EPA's efforts.

The new modeling effort presented here integrates the previous EPA PBPK model (2009) for perchlorate with the model developed by Lumen et al. (2013) for pregnant mothers and fetuses (humans) and iodide models developed by Fisher et al. (2013) for lactating rats and Fisher et al. (2016) for lactating mothers and nursing infants (humans). The model has been subjected to a quality assurance (QA) review that was conducted by Oak Ridge National Laboratory (data and parameters used) and Pacific Northwest National Laboratory (model code). The Biologically Based Dose Response (BBDR) model predicts thyroid hormone perturbations for lactating mothers, breast-fed infants and bottle-fed infants resulting from exposure to perchlorate under different dietary iodine intake levels. EPA is relying on the Lumen et al. (2013) model, peer reviewed and published previously, to predict effects for pregnant mothers and fetuses. It is important to note a modification to a key parameter was made (Michaelis-Menten constant for the sodium-iodide symporter for perchlorate, Km) and the thyroid hormone predictions were adjusted for pregnant mothers and fetuses in the model report under review.

EPA is seeking comments on the scientific rigor of the model for evaluating the effects of perchlorate on thyroid hormones in lactating mothers, breast-fed infants and bottle-fed infants under different iodine intake levels. EPA is providing access to the model program code and all necessary files to facilitate use of the BBDR model by peer reviewers and the public. EPA expects that those reviewers with the appropriate software and expertise will be able to replicate

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the results described in the BBDR model report. After completing development of the BBDR model in the acslX software, the U.S. EPA created a copy of the model that can be run in the alternate software, R. The report URL with links to the code (acslX and R versions for both the pregnancy and infant/lactation models) is:
https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/3352518

Note that the model is calibrated and expected to be valid for conditions where feedback regulation due to variations in thyroid-stimulating hormone (TSH) levels is minimal, so all charge questions regarding the model are for that range.

In March 2016, the Agency invited the public to nominate scientific experts to be considered as panelists for peer review of the draft model and accompanying report. In June, EPA announced that to achieve efficiency it was expanding the scope of the peer review to include draft approaches for application of the model to inform the development of a perchlorate MCLG. EPA has since reevaluated the review process in response to concerns that a simultaneous review of approaches for application of the model to develop a perchlorate MCLG would not allow for prior consideration of peer reviewer comments specifically on the model.

Therefore, EPA seeks public comment and peer review on the modeling approaches and the ability of the model to predict outcomes that could potentially be used to inform the derivation of an MCLG. EPA intends to seek input on the application of the model for developing approaches for a perchlorate MCLG determination at a later date. Future efforts will include discussion of health endpoints and response levels that are most appropriate to base the MCLG determination.

Charge Questions

1. Model structure: Please comment on the following aspects of the Biologically Based Dose Response (BBDR) model structure and integration of the submodels for iodide/thyroid hormones and perchlorate for each of the life stages of focus (e.g., lactating mother, breast-fed infant, and bottle-fed infant):

    a. Does the developed model structure adequately and accurately describe the physiology and kinetics of iodine, thyroid hormones, and perchlorate during different life stages specified above? Please specifically note the strengths and weaknesses of the model structure for each life stage. Please also suggest approaches to address identified weaknesses in the model structure.

    b. Are the physiological and kinetic parameters for iodine, thyroid hormones, and perchlorate for these life stages supported by the published sources for those parameters or data used to identify parameters via calibration? Please identify any critical data gaps and suggest additional data or parameter (values) to these proposed model parameters to address identified gaps.

    c. While the model predicts the dose-response for fetal thyroid hormones, a reference range for the fetus was not identified. Are there additional data, parameters, or (sub)models available that might be useful for evaluating fetal effects? If not, can the

predictions for thyroid hormone changes in the pregnant mother be used as a measure of potential fetal effects?

2. Modifications to existing models: EPA has modified one parameter in the 2013 Lumen et al. model: KM_TPNG, the Michaelis-Menten constant for the sodium-iodide symporter for perchlorate based on Schlosser (2016), and a second key parameter in the 2009 USEPA/2007 Clewell et al. PBPK models: VMAXC_MKP, the maximal velocity for perchlorate transfer to breast milk from those components in the USEPA 2009 models. These two parameters affect perchlorate transport from the mammary plasma to breast milk (VMAXC_MKP) and the strength with which perchlorate inhibits iodine transport by the sodium-iodine symporter (KM_TPNG). Detailed information on the assumptions and data considered in making these changes are provided in the report appendices. Are the changes scientifically supported and reasonably estimated?

3. Model calibration and sensitivity analysis: Please address the strengths and limitations of the model calibration process and the strengths and limitations of the data used for model calibration and evaluation. Identify any additional literature, data, or peer reviewed models that EPA should consider to address identified limitations.

    a. Specifically, is the model calibration and evaluation adequately compared with what is reported in the literature for iodine and perchlorate concentrations in urine, and breast milk and thyroid hormone plasma concentrations under different iodine intake and perchlorate exposure scenarios? Please identify additional studies that would support model calibration that strengthen the proposed model.
    b. Are the influential parameters identified in the local sensitivity analysis for total thyroxine (T4) and free thyroxine (fT4) plasma concentrations consistent with known biology? Are there critical data gaps for the influential parameters, which would impact the thyroid hormone predictions? If gaps are identified, please provide approaches that would improve thyroid hormone predictions.

    c. Does the proposed model provide the appropriate level of precision and substantiated support for this approach? Please identify any additional limitations of the model's applicability?

4. Hypothyroxinemic reference levels and model predictions: The SAB (2013) recommended that the EPA focus the application of BBDR modeling on the condition of hypothyroxinemia, in which circulating levels of free thyroxine (fT4) are reduced below the normal ("reference") range, but with normal levels of thyroid stimulating hormone (TSH). While the mode of action (MOA) for perchlorate is well described, a defined set of quantitative definitions for reference ranges for hypothyroxinemia during pregnancy or lactation and in infants is not available. For interpretation of the BBDR model, EPA developed a normalization procedure to derive hypothyroxinemia reference intervals and to control for the expected differences between literature results and model predictions.

    a. Please comment on the hypothyroxinemia reference ranges derived for pregnant mothers, fetuses, lactating mothers, breast-fed infants and bottle-fed infants. Is the assumed range between the 2.5th and 10th percentile of the fT4 distribution

reasonable? Is it supported by the available data? Has the derivation of the reference ranges, including the normalization process, been appropriately described and supported in the model and the report?

b. Model predictions for zero intake of perchlorate indicate the range of iodine ingestion for which these life-stages are expected to be euthyroid vs. hypothyroxinemic. Are these predictions reasonable and have they been appropriately described and supported in the model and the report?

c. Based on the perchlorate level at which each life stage is predicted to become hypothyroxinemic (for a given iodine ingestion rate), it appears that the lactating mother is more sensitive than the breast-fed infant for PND 30-90. In part, this occurs because breast feeding reduces the iodide available for the maternal thyroid. Are these predictions reasonable and have these predictions been appropriately described and supported in the model and the report?

5. Robustness of model predictions and sensitivity at lower perchlorate dose levels: The dose-response predictions from the BBDR model predict levels of fT4 for:
   a) The pregnant mother and fetus at GW40 (Fig. 10);
   b) The formula-fed infant with fixed (Fig. 11, 7 and 30 day infants) and variable (Fig. 12, 7 through 90 day infants) iodine levels in their formula; and
   c) The breast-fed infant as a function of maternal perchlorate exposures and iodine ingestion (Fig. 13, 7 through 90 day infants).

   For each of these subgroups, please characterize the extent of uncertainty along the dose-response curve. In particular, is the level of uncertainty acceptable at lower dose levels of perchlorate (e.g., at or below 4 μg/kg/d) and higher levels of iodine intake (e.g., 150 μg/d) for each of these subgroups (left upper corner of the dose-response curves)? Should EPA assume that the model becomes more uncertain with rising perchlorate dose levels and declining iodine ingestion, i.e., as model predictions for fT4 approach and move through the range of hypothyroxinemia. (It should be noted that calibration of the iodide and thyroid hormone sub-models used data for populations with higher iodine intake and background exposure to perchlorate.)

6. Empirical functions to predict thyroid hormone levels: The pregnancy model (but not the lactation/infant models) uses empirical functions to make urinary clearance of iodine and metabolic degradation of T3 dependent on the iodine ingestion level, in order to predict observed nonlinearity in the relationship between thyroid hormone levels and iodine intake. Does this use of empirical functions result in predicted outcomes or trends that are not plausible for serum thyroid hormones, particularly fT4?

7. Characterization of model predictions: The pregnancy and infant/lactation models were developed to specifically consider the range of iodine ingestion and thyroidal uptake where TSH is expected to stay in its normal range (i.e., they do not account for HPT feedback control). Do the models represent a reasonable effort to describe the relationships between iodine intake, perchlorate exposure and thyroid function? Are they sufficiently specific to predict perchlorate-induced changes in thyroid hormones in these life-stages over the range indicated? Please characterize the robustness, precision and sensitivity of the models for the

ability to extrapolate changes in T4 associated with perchlorate exposures over the range from low exposures (less than 1 μg/kg/d) to higher levels which the model and analysis predict to be hypothyroxinemic.

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III. GENERAL IMPRESSIONS

Hugh A. Barton, Ph.D.

Overall, this is an extensive systems model that appears to have been carefully and thoroughly developed using available scientific information. The report could be clearer, though the logic of the decisions presented seems reasonable. It is difficult to evaluate a model of this complexity by reading the report. This reviewer did not access the model, but in my experience it would take considerable time working with a model of this complexity to develop perspectives on its strengths and limitations. Finally, the absence of a clear description of how the model and its outputs would be used in the risk assessment process makes it difficult to evaluate whether the model is fit for purpose. Models can always be improved, but the question needs to be whether the model is ready for the intended.

Claude Emond, Ph.D.

This peer review is part of the U.S. Environmental Protection Agency's (EPA's) National Primary Drinking Water Regulations (NPDWR) initiative for perchlorate a water contamination. This review is also the second phase of Science Advisory Board (SAB) 2013, which recommended that EPA should use a physiologically based pharmacokinetic (PBPK) model published earlier, but should integrate the iodine description, including the hormones T3 and T4, to study the hypothyroxinemia and health effects after exposure to perchlorate during lifetime and windows of sensitivity. Two models are presented here 1) mother and fetus PBPK model, and 2) mother and infant. Both integrate the previous model of perchlorate that was published and used for the SAB assessment in 2009. These improving version integrated the iodine/thyroid pharmacokinetic for different stages of life, including the fetus, newborn until 91 days, pregnancy or no pregnancy, and lactation. This report is very well described and transparent, and very well referenced for the model code part, but there is a little fogginess for the m files. The methodology that was used reflects state-of-the-art pharmacokinetic modeling. I agree that this model is a good start to better understand the mode of action, including the limiting step that we know from literature today. The authors who developed this PBPK model are very knowledgeable in the design of PBPK models. Based on confidence of the design, and the review that I performed, the combined PBPK model for iodine/perchlorate exposure following sensitive lifetime windows can be used for human risk assessments of health, with the limitation suggested by the authors. It is interesting to note that the authors also reported a limitation of the PBPK model regarding the range of dose and the windows of sensitivity. I agree with the authors' conclusions regarding the predictability and the limitations of this model. It is important to remember that these models are described for human exposure, which should drastically reduce the uncertainty of the point of departure (POD) used in risk assessment. In addition, the simulations reviewed in this report reproduced relatively well the biomonitoring data published.

Dale Hattis, Ph.D.

Although I have some concerns about the parameterization of the models, my most serious problems with the analysis relate to the choice of population to be modeled and the endpoints that were made the focus of the analysis.

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Briefly, in focusing on thyroid hormone changes, the authors have neglected the prime effect of ultimate interest—changes in cognitive development measured as IQ. The latter will need to be a key focus in the mandated "Risk Reduction and Cost Analysis (HRRCA)" referred to in the introduction. IQ differences are readily subject to the comparative economic analysis needed for an HRRCA, whereas it will be difficult to quantify the independent value of thyroid hormone changes themselves for juxtaposition with compliance and other costs of alternative regulatory actions to change exposures. Moreover, studies in the very recent literature, such as those from Holland, provide an excellent basis to quantify effects of both thyroid hormone changes[1] and perchlorate itself[2] during pregnancy on cognitive function as reflected in the IQ measured in the offspring.

Additionally, the focus on modeling of changes in thyroid hormone levels has led the authors to focus their analysis on lactating mothers and breast- and formula-fed infants after birth. This neglects the population groups that are known to be most sensitive to the effects of iodide and thyroid hormone action-women in the first pregnancy trimester, and possibly even the first month of pregnancy before the women may even be aware that they have conceived.[3,4,5]

The Specific Observations on Model Report, at the end of these comments, provides abstracts of recent papers that I think should be used in crafting a better analysis more relevant to EPA's needs in choosing policies to change the existing exposures to perchlorate in the United States.

[1] Korevaar, TIM, Muetzel, R, Medici, M, Chaker, L, Jaddoe, VWB, de Rijke, YB. 2016. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. The Lancet Diabetes-endocrinology 4:35-43.
[2] Peter N. Taylor, Onyebuchi E. Okosieme, Rhian Murphy, Charlotte Hales, Elisabetta Chiusano, Aldo Maina, Mohamed Joomun, Jonathan P. Bestwick, Peter Smyth, Ruth Paradice, Sue Channon, Lewis E. Braverman, Colin M. Dayan, John H. Lazarus, and Elizabeth N. Pearce. 2014. Maternal Perchlorate Levels in Women With Borderline Thyroid Function During Pregnancy and the Cognitive Development of Their Offspring: Data From the Controlled Antenatal Thyroid Study J Clin Endocrinol Metab 99:4291-4298.
[3] Morreale de Escobar, G, Obregon, MJ, Escobar del Rey, F (2000). Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia? J. Clinical Endocrinology and Metabolism 85: 3975-3987.
[4] Cao, XY, Jiang, XM, Dou, ZH, Rakeman, MA, Ming-Li, Z, O'Donnell, K, Tai, M, Amette, K, DeLong, N, DeLong, R. 1994. Timing of Vulnerability of the Brain to Iodine Deficiency in Endemic Cretinism. New Engl. J. Med 331:1739-44
[5] Bath, SC, Steer, CD, Golding, J, Emmett, P, Rayman, MP. 2013.Effect of Inadequate Iodine Status in UK Pregnant Women on Cognitive Outcomes in their Children: Results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

Angela M. Leung, M.D., M.Sc.

The objective of this proposed BBDR model was to assess the potential adverse thyroidal effects of perchlorate exposure, based on the physiologic kinetics of perchlorate and iodide action on serum free thyroxine (FT4) concentrations among lactating women, their breastfed infants, and formula-fed infants. Calibration of the model was achieved using published levels of perchlorate

and iodine found in breastmilk, maternal urine, and infant urine, and of serum FT4 concentrations in each of these three lifegroups. The model's dose-response relationships between perchlorate exposure and serum FT4 concentrations are reported for various perchlorate exposure and daily dietary iodine intake levels.

The primary endpoint was hypothyroxinemia, defined as the 2.5-10th percentile of serum FT4 concentrations, among lactating women, breastfed infants, and formula-fed infants. Overall, there is less robust evidence in the literature to support the adverse health implications of mildly low serum FT4 concentrations among infants regarding future neurodevelopmental outcomes, compared to the same for pregnant women, in part due to complete reliance of the fetus on adequate maternal iodine and thyroid hormone levels during the first half of pregnancy and the crucial period of rapid neurodevelopment during this time.

The second concern is in regards to the interpretation of published data regarding iodine and perchlorate levels in breastmilk, maternal urine, breastfed infant urine, and formula-fed infant urine; and serum FT4 concentrations in lactating women, breastfed infants, and formula-fed infants. The accuracy of calibration of the model is limited by several issues, including: 1) the use of several relatively small studies containing limited datapoints, particularly for maternal serum thyroid hormone concentrations, 2) the absence of serum thyroid autoantibody data that can influence serum thyroid hormone concentrations, 3) the problems of extrapolation of pregnancy thyroid hormone physiology for the lactation model, 4) the absence of data regarding the timing of dietary iodine intake in relation to breastmilk iodine concentrations in the current available literature, and 5) the inference of analyte and hormone measurement values in the submodels that each assume an exclusive source of infant iodine nutrition.

Finally, the model does not take into account likely coexposures from other environmental and dietary goitrogens, including thiocyanate and nitrate, and it does not consider the dynamics of the hypothalamic-pituitary-thyroid (HPT) axis that is able to respond acutely to even small changes of iodine availability and peripheral thyroid hormone concentrations. Given all of the above and as summarized in much greater detail below, the model presents an estimate of the potential thyroidal effects resulting from perchlorate exposure, but is likely still fairly inexact.

For the record, I am a clinical endocrinologist with research interests in iodine nutrition and environmental thyroid disruptors during pregnancy and lactation, but do not have sufficient background and expertise in modeling to comment on the charge questions that specifically address those aspects of the model.

Michael H. Lumpkin, Ph.D., DABT

The developed model structure adequately captures the known biological processes acting to exchange iodine, TH, and perchlorate across tissue interfaces and transport these molecules across tissue systems and out of the body. The report describes well the representation of the biology in the mathematical model structure. The report describes in detail the selection of data that serve as the basis of model parameter values for the various life stages. This includes the consideration of data published or made available since publication of the foundational BBDR and PBPK models for perchlorate. The justifications for modifying the saturable NIS physiology and NIS transport of iodide and perchlorate into breast milk using more robust data are

sufficiently supported in the model report. Given the model structure changes required to align the perchlorate PBPK and iodine BBDR models, the need to revisit the model's fidelity to replicate the Greer et al. data was warranted. The model performance across the various represented life stages appears to be robust for low perchlorate exposures and iodide intake levels resulting in thyroid hormone levels above the 10th percentiles for the reference ranges. The model is likely restricted in its utility for risk assessment due to the lack of the 1st trimester life stage. Further, the lack of TSH feedback control in the model may have important implications for its use in risk assessment.

Elizabeth N. Pearce, M.D., M.Sc.

The clarity of the writing could be improved; the document is complex and hard to follow. Many of the figures are challenging to interpret: both duplicating information in tables and providing color figures would be helpful. More explanatory legends would also be useful; the figures were better understood after the detailed explanation at the peer review meeting. A single glossary including a list of all of the variables as well as the list of abbreviations would be useful for reference.

A more detailed rationale for the choice of hypothyroxinemia as the primary outcome of interest could be provided in the Introduction. This is fundamental for understanding the document which follows.

The literature search, as described on page 22, should be updated. There has been a great deal of new literature since 2013 with relevance to effects of perchlorate on thyroid function and other outcomes in epidemiologic studies; many new pregnancy cohorts in the literature have described thyroid function reference ranges; there are new iodine balance study data for formula-fed infants; and there are many new observational studies regarding effects of maternal hypothyroxinemia on child developmental and other outcomes. Although it may be too late to incorporate newer data into model parameters, some of these new studies could provide support for the selection of hypothyroxinemia as the outcome of interest, and many could provide valuable data for further calibrating models.

Please note that my expertise is in clinical thyroidology and iodine metabolism. I do not have expertise specifically in the development or use of BBDR modeling. While I comment below on many of the assumptions that went into the models and the data used to validate them, I will need to defer to other peer reviewers with modeling expertise regarding the model code.

Stephen M. Roberts, Ph.D.

It is apparent that a great deal of work has been conducted to develop a proposed BBDR model that is responsive to recommendations made by the SAB Perchlorate Advisory Panel. There are many strengths to the model and its intended use in developing a MCLG for perchlorate, including:

- It is based on a consensus mode of action (MOA) for perchlorate effects involving inhibition of iodine uptake by the thyroid leading to thyroid hormone deficiency
- It is based upon iodine and perchlorate toxicokinetics in humans

- It addresses the most sensitive life stages
- It is based on protection from a serious, unambiguous adverse health effect known to occur in humans (neurodevelopmental deficits) associated with thyroid hormone deficiencies

Although some improvements in the model and documentation can and should be made, as discussed in these comments, it is important to keep in perspective the unique advantages to this approach in reducing uncertainty in risk estimation compared with the typical approach for most chemicals.

I found the information presented in the report to be accurate for the most part, but clarity in presentation is lacking. Dialog with EPA during the face-to-face meeting provided the opportunity to resolve many questions raised in reading the report, but it is important for the report to be as transparent as possible. It was apparent during the face-to-face meeting that other panel members also found the report to be confusing and unclear. As a result, many of the charge questions to the panel could not be effectively answered. If the clarity is not improved, it is reasonable to expect a similar reaction among others engaged in the MCLG process, compromising acceptance of the model. Both the model and the associated biology are complex, which makes producing a readable report challenging, but even more necessary than would be the case for a simpler model and issue.

In addition to a general improvement in clarity of presentation, the document needs to include explanations for critical choices in model construction. Explanations exist to some extent, but there are important issues that are not discussed, especially related to aspects of iodine and perchlorate biology that were <u>not</u> included in the model. As Dr. Emond pointed out in the face-to-face meeting, a model is never done, and as a practical matter a decision must be made at some point to use the model as is and make additional refinements in future iterations. This is generally understood. In my opinion, it will be important to include in the report explanations why certain aspects raised by public commenters and in panel discussions were not part of this iteration of the model. Examples include co-exposure to other goitrogens, compensatory effects in response to perchlorate inhibition, and probabilistic inputs. There can be a number of legitimate reasons why possible inclusions or refinements in the model were not chosen for this iteration of model development, including limitations in time, resources, and/or data availability, or their addition was thought unlikely to significantly improve the model. Discussing these issues, however briefly, will be important for the EPA to make a case in the report why the current model is "fit for purpose."

Another general impression is that the model was constructed with limited input from experts in thyroid endocrinology in humans. This impression is based upon critical comments made by the thyroid experts on the panel during the face-to-face meeting regarding certain aspects of the model and its output. Going forward, it would useful for the EPA to periodically access individuals with this expertise to make sure that the model and its outputs are consistent with current clinical concepts in iodine deficiency, thyroid hormone status, and associated neurodevelopmental deficits.

A related general impression is that the model is not well informed by recent literature. This was acknowledged by EPA during the face-to-face meeting, where it was indicated that the primary

effort since 2013 was on the task of developing the model — especially on modeling the effects of iodine and perchlorate intake on thyroid hormone status in breast fed and formula fed infants. This focus is understandable given the complexity of the task, and every analysis has to employ a cut-off for new information as a practical matter. However, a three-year gap in knowledge is a pretty long one, and as Dr. Pearce pointed out in the face-to-face meeting, the literature on iodine and thyroid hormones in pregnancy, and on neurodevelopmental outcomes, has exploded in the last three years. I am NOT suggesting that EPA do a systematic literature search of the type now used for toxicological reviews for IRIS, for example, given the time and expense involved. However, it is likely that the newer literature contains reports that may be useful for re-calibration, or at a minimum, evaluation of model output. The EPA should consider conducting a focused search of literature from 2013-2016 for papers of papers of potential value, and of course examine papers identified as potentially useful by members of this panel. During the meeting, Drs. Pearce and Leung both offered the EPA access to raw data that conceivably would be useful for model calibration and/or evaluation. I encourage the EPA to take advantage of their offer.

Joanne F. Rovet, Ph.D.

EPA has requested comments on the scientific rigor of a BBDR model for predicting thyroid hormone perturbations for lactating mothers and breast-fed and bottle-fed infants following their exposure to perchlorate at different levels of dietary iodine intake. This model is an expansion of the one described in a peer-reviewed paper by Lumen et al. (2013) predicting effects for pregnant mothers and fetuses. The current model seeks to address the main recommendations of a Science Advisory Board-Perchlorate Advisory Panel (SAB-PAP) for developing a maximum contaminant level goal or safe perchlorate exposure level for the following sensitive life stages: fetus, pregnant woman, and breast- or formula-fed infant. The PAP group considered these life stages particularly sensitive to perchlorate effects since they reflected stages when the greatest harm from an insufficiency of thyroid hormone would occur to the developing human brain. The pregnant woman was included as a sensitive life stage since she was considered a surrogate for providing thyroid hormone prior to onset of fetal thyroid function when thyroid hormone is critically needed for fetal brain development; the pregnant woman was also considered a supplementary or complimentary source of thyroid hormone in later gestation prior to full function at term.

The current modeling process claims -- for the first time -- to offer a BBDR approach that calculates the adverse consequences of a particular level of perchlorate exposure. Perchlorate is a potent inhibitor of iodide, a key component of thyroid hormone, and is taken up by the maternal, fetal, or infant thyroids or the lactating breast. The model's authors have conceived a reasonable, relatively simple model of biological action and from the literature, have provided an extensive set of realistic parameters and metrics to track the biological actions. These ultimately determine when an infant or lactating mother will become hypothyroxinemic from a specific level of perchlorate in a specific iodine environment. Authors are to be commended for their thorough, systematic, and ambitious approach to capture the situation, particularly on the perchlorate-iodide side of the equation.

However, I have several reservations about the approach and certain assumptions, leading me to sense some naiveté and perhaps lack of understanding on the part of the modelers. First, I am not

convinced that the fT4 range used to mark hypothyroxinemia is appropriate and, rather, is too lenient. There is no evidence of what constitutes hypothyroxinemia in an infant and what the exact cut-offs are; these are all based on values from pregnant women. I am also concerned that the thyroid-side of the system may be too simplistic and not correct; the HPT axis, for example, is not modelled. Perchlorate contamination in the water used to prepare formula is not included in the model despite being mentioned in the SAB-PAP (2013) report. The key critical stages set out in the latter, namely pregnant mother and fetus, are for reasons that I do not find convincing disregarded, even though these stages are included in the title and extrapolated in the results; however, I am not sure how this was done. Also, the primary downstream endpoint, namely altered brain development and associated cognitive abilities and behavioral factors, is never considered. The modelling itself is based on old references, which I find concerning in light of the many papers on maternal thyroid dysfunction in pregnancy that have been published in recent years. The process whereby the ultimate 6 papers were selected from the final 62 is not specified. I also would have liked a better description of each of the papers, even if in the Appendix, than the current summary in Table 2. In addition, the model does not account for other contaminants such as thiocyanate and nitrates that similarly interfere with iodide uptake. The data for the lactating women assume a common start point with regard to iodide sufficiency; however, no attempt is made to examine factors in pregnancy that might also contribute to iodide differences in the breast such as salt intake, particularly iodized salt; dietary factors (kelp, fish, amount of drinking water); use of iodine-containing prenatal vitamins and other supplements; amount of weight gained by mother and size of baby.

Additionally, I was disappointed in the lack of transparency on derivation of results and found the results section, especially the figures, which are relatively poor quality, hard to interpret. The latter aspect is particularly disheartening given the beautiful graphics supplied by "R". To improve clarity, all figures also would have benefited significantly by better more extensive figure captions. Overall, I found the Results section very poorly organized and hard to follow, very preliminary and rushed, almost as a first draft. It was not clear to me how data on pregnancy and fetal development were derived. While somehow, I think this is extrapolated back to birth at 40 weeks' gestation, to me this does not adequately represent the period of pregnancy nor fetal life. The writing generally carried a degree of vagueness (e.g., "adequate" p. 60; "within the range" p. 62) and lack of precision and it was generally quite difficult to follow the information in the figures from the corresponding text. Finally, as there was no proper ending to the report and no conclusions or take-home message, I was left with a sense of confusion – and disappointment. This was especially apparent in the Local Sensitivity Analysis that lacked proper discussion. This report should be readily understandable by persons of all disciplines; I sense it is written mostly for modelers and sometimes in modelling lingo.

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IV. RESPONSE TO CHARGE QUESTIONS

Question 1. Model structure: Please comment on the following aspects of the Biologically Based Dose Response (BBDR) model structure and integration of the submodels for iodide/thyroid hormones and perchlorate for each of the life stages of focus (e.g., lactating mother, breast-fed infant, and bottle-fed infant):

Question 1A. Does the developed model structure adequately and accurately describe the physiology and kinetics of iodine, thyroid hormones, and perchlorate during different life stages specified above? Please specifically note the strengths and weaknesses of the model structure for each life stage. Please also suggest approaches to address identified weaknesses in the model structure.

Hugh A. Barton, Ph.D.

This question really requires expertise in thyroid hormone, iodine, and perchlorate biology. As an expert in modeling I cannot directly comment on how well the model structure captures the biology.

As discussed at the peer review meeting, addressing earlier periods of pregnancy, not just term, is important as there appears to be good data relating maternal hormone levels in this period to neurodevelopmental outcomes in offspring. This may require changes in the structure and/or a modified parameter set. Dr. Joanne Rovet raised specific concerns around the description of the deiodination from T4 to T3 and reverse T3, so it would be valuable to review this aspect, although it would be appropriate to focus on modeling maternal levels during pregnancy and may not be necessary to describe fetal hormones levels given the limited data and likely major uncertainties associated with that.

One question raised in the public comments was whether there were regulatory processes that would occur at low iodine and T4 levels, such as induction of NIS. It would be good to know whether there is information on this point. As discussed at the meeting, ideally a model would describe the complex feedback regulation among iodine, TSH, T4, and other hormones allowing it to predict both isolated thyroxinemia and hypothyroidism. Given the challenges and undoubtedly substantial efforts required to incorporate this feedback, it appears reasonable to utilize a modified version of the current model applicable to isolated thyroxinemia.

Another question raised in public comments about the model structure was the change from a three compartment thyroid to a two compartment description. From the text on p. 30, it appears that having a consistent structure in the fetal (Lumen et al., 2013) and the infant models might have been part of the rationale for this change. This could be clarified and perhaps some information provided as to the value provided by the three compartment description in previous modeling by comparison with this two compartment approach; was this a model simplification that had relatively modest impacts on model behaviors or was this a more substantial change or is this not known?

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Claude Emond, Ph.D.

Strengths:

- The way in which the authors describe the codes in acslX in the 2 models was relatively easy to follow and well referenced for the CSL file.
- Comparing the simulation to the biomonitoring data from the literature, we can say that the predictability of the model is acceptable.
- The confidence in the models should be qualified by a medium that is inside the limitation of the model.

Weaknesses:

- The conceptual PBPK model structure (Figure 3) does not describe what the codes represent. The model codes describe kidney, liver, mammary gland, GI_{tract}, skin, and thyroid and so on. It should be easier to incorporate these compartments inside of Figure 3.
- The way the codes are described, it seems that there is interlace between several models in unique code files. This can be a problem if some users are inexperienced; therefore, users of the model must have previous experience with models in order to use the combined version.
- It would be also interesting in the future to incorporate mother, fetus, lactation and infant in the same model.
- Even though the 'csl' files are good, the ''.m'' files are trickier. For me, this part misses the objective of transparency. The 'm' files can reproduce the graph cited in the report, but it is difficult to understand the logic simulation behind it. It will be important for the upcoming user to understand the mechanics behind the result.
- If I have not missing something, it seems that the fetus model has a fixed constant (3.4 kg) for body weight. It does not consider all the fetus formation but only the week 40th. Is there a rational behind this or it is due to a lack of data?

Dale Hattis, Ph.D.

As indicated above, I disagree with the focus on the specific life stages chosen for detailed analysis. If the shift is made to quantifying cognitive impairment rather than just thyroid hormone level changes, as I recommend, I think it would be much better to model fetal and maternal perchlorate effects on perchlorate and thyroid hormone levels in early pregnancy.

There are no obvious problems with the model structures used to describe these kinetics.

Angela M. Leung, M.D., M.Sc.

Comments regarding physiology and kinetics of the model structure:

The focus of the overall model is the potential adverse effect of perchlorate exposure in the lactating mother and in the infant (both breastfed and formula-fed) during ages days 7-90 of postnatal life. The model considers the kinetics of and physiology between perchlorate exposure, dietary iodine nutrition, and serum thyroid hormone concentrations in the lactating mother,

breastfed infant, and formula-fed infant. The primary endpoint is hypothyroxinemia, defined as the 2.5-10th percentile of serum FT4 concentrations among lactating women, breastfed infants, and formula-fed infants. Some general comments are as follows:

- It would be reasonable to consider the full HPT axis, given the interdependence of serum TSH and FT4 concentrations on the changing effects of iodine nutrition and perchlorate exposure. The assessment of serum FT4 concentrations in isolation is a limitation of the physiologic responses that occur with dynamic variations of iodine supply, as incurred with constantly changing dietary intake, breastfeeding, and urinary excretion.
- The role of coexposures by other environmental toxicants, such as thiocyanate and nitrate, should be assessed in reference to the effects of perchlorate during these life stages. The potency of perchlorate, relative to thiocyanate and nitrate, as a competitive inhibitor of iodine at NIS should be considered.
- The long-term concern of perchlorate exposure during crucial periods of early development is on the possible detrimental neurocognitive effects among exposed fetuses and infants. The current literature surrounding the associations of maternal hypothyroidism and/or hypothyroxinemia on later offspring neurodevelopment is generally better-established than that for infant hypothyroxinemia.

Regarding the applicability of the model for each of these three life stages:

a. **Lactating mother**: Perchlorate exposure in the lactating woman is assumed to be from ingestion through the diet. The present model reflects an integration of the previous PBPK perchlorate models predicting thyroidal RAIU inhibition with the PBPK iodine and BBDR thyroid hormone models, which were based on the previously published pregnancy model. For the analyses, maternal iodine intakes are assumed to range between 75-250 mcg/day, and maternal perchlorate exposures up to 20 mcg/kg/day are assessed. For reference, major points reviewed are:
    - The previous *pregnancy* model (page 18, lines 1-13) assumed dietary iodine intakes of >200 mcg/day, but notes that model dose-response predictions for iodine intakes ≥150 mcg/day are judged to be similarly reliable, given the very small decrease in serum FT4 concentrations between the two levels. The pregnant mother also was predicted to have a lower baseline serum FT4 concentration (in the absence of perchlorate) than the lactating mother at postnatal day 7, given the same amount of dietary iodine.
    - The *lactating* model (page 18, lines 20-25) assumes dietary iodine intakes of >250 mcg/day, but notes that model dose-response predictions for iodine intakes ≥150 mcg/day are judged to be similarly reliable, given the very small (6-14%) decrease in serum FT4 concentrations between the two models. At postnatal days 7-90, the lactating mother's serum FT4 concentrations are predicted to decrease due to the physiological changes and demands of breastfeeding.

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- At postnatal day 7 for the lactating mother, the steepness of the perchlorate dose-response for maternal serum FT4 concentrations is similar to that for the pregnant mother. The model predicts that if maternal perchlorate exposure is <4 mcg/kg/day, both the pregnant and lactating mother maintain normal serum FT4 concentrations if their dietary iodine intakes are at least >150 mcg/day.
- Sensitivity analyses suggest that maternal parameters impacting breastmilk iodine concentrations, amount of breastmilk ingestion, and kinetics of thyroid hormone physiology and urinary excretion of iodine are important predictors of serum FT4 and TT4 concentrations in the breastfed infant.
- The maternal sub-model as shown in Figure 3 was reviewed in detail for this question.

- **Strengths**:

1-- The model considers available published data regarding iodine, perchlorate, and serum FT4 physiology and concentrations during pregnancy, lactation, and early infancy, though with several important caveats.
2-- With the exception of the comments below, the maternal sub-model addresses the kinetics of iodine and thyroid hormone physiology during lactation.

- **Weaknesses**:

1-- Maternal urinary iodine levels are not accounted for in the maternal sub-model as shown in Figure 3. There are data reporting that estimated urinary iodine 24-hour excretion in the mother, rather than spot maternal urine iodine concentrations, are a good reflection of maternal iodine supply to the breastfed infant (Andersen SL et al; PMID 2419933); these data also demonstrate that breastmilk iodine concentrations are not correlated with maternal fluid intake.
2-- Also not shown in Figure 3 is the active transport and concentration of perchlorate into mammary cells during lactation by NIS (Dohan O et al; PMID 18077370), which is significant for the potential of perchlorate exposure from breastmilk to directly inhibit the infant's thyroidal iodine uptake.
3-- The relative potency of perchlorate as a competitive inhibitor of iodine uptake at NIS (30:1 affinity to iodine) should be included (Tonacchera et al; PMID 15650353).

b. Breastfed infant: Perchlorate exposure in the breastfed infant is assumed to be from breastmilk ingestion and focuses on the effects of exposure during postnatal days 7-90. For reference, major points reviewed are:

- At postnatal day 7, the perchlorate threshold associated with breastfed infant serum FT4 concentrations decreasing to below the lower limit of the reference range is 12 mcg/kg/day.
- During postnatal days 7-90, the model predicts that maternal perchlorate exposure reduces breastfed infants' serum FT4 concentrations, with the magnitude of decrease inversely dependent on maternal dietary iodine intake.
- During postnatal days 30-60, breastfed infants' serum FT4 concentrations would be predicted to remain within the reference range when maternal dietary iodine intakes are ≥150 mcg/day and maternal perchlorate exposure is <20 mcg/kg/day, even though maternal thyroid function is expected to be abnormal (hypothyroxinemic or hypothyroid) in these ranges.

- Overall, the model predicts a larger effect on serum FT4 concentrations in breastfed infants than formula-fed infants, due primarily to the higher perchlorate concentrations in breastmilk than infant formula in general; this discrepancy is then further exacerbated when breastmilk iodine content is low from insufficient maternal dietary iodine intake.
- The infant sub-model as shown in Figure 2 was reviewed in detail for this question.

- **Strengths:**

1-- The model considers data from the existing literature regarding iodine, perchlorate, and serum FT4 physiology and concentrations during lactation for the breastfed infant.

- **Weaknesses:**

1-- Similar to the comment above regarding the lactation mother, what is not shown in Figure 2 is the active transport and concentration of perchlorate into mammary cells during lactation (Dohan O et al; PMID 18077370), which is significant for the potential of perchlorate exposure from breastmilk to directly inhibit the infant's thyroidal iodine uptake.
2-- Perchlorate inhibition (as shown in yellow in Figure 2) might be better clarified if the potential sources of perchlorate exposure in the breastfed infant were also shown (i.e., breastmilk, formula), similar to what is shown for sources of iodine.
3-- One major limitation is the significant variability of breastmilk iodine concentrations in the existing literature upon which the model is built. Please see my comments in Question 1B regarding this.
4-- The recommendations for dietary iodine intake in infants should be referenced. The U.S. Institute of Medicine estimates that the Adequate Intake for infants ages 0-6 months is 110 mcg iodine/day. This is based on iodine turnover studies showing that iodine requirements in term infants is 15 mcg/kg/day (Comprehensive Handbook of Iodine, 2009).

c. **Formula-fed infant**: Perchlorate exposure in the formula-fed infant is assumed to be from infant formula ingestion and focuses on the effects of exposure during postnatal days 7-90. For reference, major points reviewed are:
    - For all postnatal days and infant formula iodine concentrations studied (108-384 mcg/L), the model predicts infant serum FT4 concentrations to stay within the reference range.
    - Perchlorate exposure from infant formula would be expected to reduce infant serum FT4 concentrations at postnatal day 7, but not between postnatal days 30-90, for all infant formula concentrations.
    - The infant sub-model as shown in Figure 2 was reviewed in detail for this question.

- **Strengths:**

1-- The model considers data from the existing literature regarding iodine, perchlorate, and serum FT4 physiology and concentrations during lactation for the formula-fed infant.
2-- The infant model was developed on the assumption that the iodine content of infant formulas ranges from approximately 100-300 mcg/L. Thus, for the described kinetics of infant formula intake, these infant formula iodine concentrations are predicted to be sufficient for normal thyroid hormone production in the formula-fed infant (page 18, lines 14-17).

- **Weaknesses:**

1-- The infant sub-model as shown in Figure 2 does not show the potential of perchlorate exposure that can also occur from infant formula ingestion (Pearce EN et al; PMID 17311853).
2-- Perchlorate inhibition (as shown in yellow in Figure 2) might be better clarified if this potential source of perchlorate exposure in the formula-fed infant was also shown, similar to the what is shown for sources of iodine.
3-- The recommendations for dietary iodine intake in infants should be referenced. The U.S. Institute of Medicine estimates that the Adequate Intake (an estimation of the Recommended Daily Allowance [RDA] when there are insufficient data) for infants ages 0-6 months is 110 mcg iodine/day. This is based on iodine turnover studies showing that the iodine requirement in term infants is 15 mcg/kg/day (Comprehensive Handbook of Iodine, 2009).

Michael H. Lumpkin, Ph.D., DABT

The developed model structure adequately captures the known biological processes acting to exchange iodine, TH, and perchlorate across tissue interfaces and transport these molecules across tissue systems and out of the body. The report describes well the representation of the biology in the mathematical model structure. The use of volumes of distribution for maternal and fetal thyroid hormone concentration calculations is an acceptable means of representing the presence of thyroid hormone levels outside of the thyroid itself, as thyroid hormone impacts multiple organ systems rather than a single target organ. For the life stages listed in the charge questions, and recommended by the SAB (2013), the model structure is adequate to predict pharmacokinetic/dynamic interactions between perchlorate and NIS in the thyroid and other tissues for a narrow range of perchlorate dose levels.

The report does not explain the decision to restrict the modeled period of pregnancy to parturition only. There are data indicating that the 1st trimester is a particularly sensitive life stage for the developing fetus in terms of adequate thyroid hormone availability and neurological development.

A second important gap in the BBDR model that may have important implications for its use in risk assessment is the lack of TSH expression and feedback control. It is understood that mathematically simulating hormonal feedback processes such as the Hypothalamus-Pituitary-Thyroid (HPT) axis, using discrete physiological/biochemical parameters or empirical functions, is technically complex and daunting, and may not be plausible in the case of the HPT axis due to data gaps. However, the present BBDR model operates under the assumption that TSH expression (indicating onset of hypothyroidism) discretely activates in a population when the average plasmaT4/fT4 levels drop to the 2.5th percentile. If TSH expression begins in a population closer to the 10th percentile plasmaT4/fT4 levels than the 2.5th percentile levels, upregulation of NIS activity may result in a "shallowing" of the dose response curve at the interface of the proposed euthyroid/hypothyroxemic interface.

Elizabeth N. Pearce, M.D., M.Sc.

Although the choice of hypothyroxinemia as the primary outcome of interest was previously established by the SAB, the strengths and weaknesses of this approach at each life stage deserve consideration.

Strengths of this approach include efforts to identify both the particularly vulnerable life stages and the most significant public health outcomes which are potentially associated with perchlorate exposure. In thinking about the potential public health impact of perchlorate exposure, potential adverse outcomes essentially overlap those of iodine deficiency, and the potential adverse effects on fetal and child neurodevelopment are of paramount interest. There are relatively few data at present to support an effect of maternal subclinical hypothyroidism on lowered child IQ (a study by Haddow et al. included both overtly and subclinically hypothyroid women: Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555). However, there is a growing body of evidence demonstrating adverse child developmental effects of maternal hypothyroxinemia in pregnancy (in addition to those cited in the report, see papers listed below under 3A). Importantly, these studies have assessed maternal free T4 in early to mid-gestation; links with third-trimester maternal hypothyroxinemia have not been established. Therefore, extending the model to cover all three trimesters would be highly valuable.

There are some limitations regarding the choice of hypothyroxinemia at certain life stages as the primary outcome of interest. Despite the observational data suggesting a link between early gestational maternal hypothyroxinemia and adverse child developmental outcomes, there are now two randomized clinical trials (Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ 2012 Antenatal thyroid screening and childhood cognitive function. N Engl J Med 366(6):493-501 and http://www.ajog.org/article/S0002-9378(15)01319-8/pdf) which demonstrate no benefit of levothyroxine treatment for maternal hypothyroxinemia on child IQ. (It is worth noting that both of these trials were limited by relatively late initiation of therapy; at 13 weeks in CATS and at 17 weeks gestation in the Casey study.) Given both the lack of interventional data demonstrating treatment benefit, and the challenges of establishing maternal free T4 reference ranges and treatment targets, current clinical guidelines (including newly-published updated guidelines from the American Thyroid Association: Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman W, Laurberg P, Lazarus JH, Mandel SJ, Peeters R, Sullivan S. 2016 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315-389. doi: 10.1089/thy.2016.0457) largely recommend against levothyroxine treatment for isolated maternal hypothyroxinemia. In addition, in lactation, maternal hypothyroxinemia has not been defined as a clinical syndrome and has not been linked to any adverse outcomes. Therefore, normative reference ranges for thyroid function tests specifically in lactation have not been established. Infant hypothyroxinemia might lead to impaired neurodevelopment, but data for normal free T4 ranges in infants are limited.

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The lack of consideration of the HPT axis in the BBDR model is a very substantial limitation of the model at each life stage. Clinically it is virtually never appropriate to interpret free T4 in isolation, without consideration of the serum TSH and other thyroid function test values. The rationale of the model creators, that TSH will remain stable over the free T4 range of interest, is counter to findings typical in clinical practice. Because of the log-linear relationship between TSH and free T4, generally in mild thyroid failure the free T4 will initially remain relatively stable while the TSH climbs. The 1981 paper by Silva & Silva, upon which assumptions about the stability of TSH over the free T4 range of interest were based, is problematic. TSH measurements in that paper were made using a first-generation TSH radioimmunoassay. These assays have long been phased out of clinical practice due primarily to insensitivity of the assay at the low end of TSH. The limit of detection for the TSH assay used in the Silva paper is not described, but typically such assays could only detect TSH down to a lower limit of about 1 mIU/L (modern assays can detect levels down to at least 0.01 mIU/L; this is important because the low end of the normal range for TSH in early pregnancy is about 0.1 mIU/). In addition, maternal thyroid function is expected to vary in a standard fashion over the course of gestation (see. e.g., D Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 1997;18(3):404-33). These expected changes were not observed in Silva & Silva, suggesting to me that there may have been problems with the peripheral thyroid hormone assays as well as with measurement of TSH in that study. In general, decreases in thyroid hormone stimulate increases in TSH; higher TSH levels, in turn, will increase the affinity of the thyroid for iodine uptake, increase the ratio of T3 to T4 synthesized by the thyroid (which may have important implications for the fetus, given that transplacental passage of maternal thyroid hormone is primarily of T4, not T3), and cause thyroid hyperplasia. There is also a good deal of interpersonal variation in compensatory mechanisms, so that I am not sure it is fair to state (as on page 69) that hypothyroidism is expected when the free T4 drops to the 2.5th percentile.

It is notable that environmental exposures to perchlorate do not occur in isolation; exposure to thiocyanate and nitrate is equally ubiquitous and works by the same mechanism of NIS inhibition. It, therefore, would seem potentially pertinent to include variable co-exposure to thiocyanate and nitrate in the models. Given available data in the literature about exposures at different life stages (e.g. from NHANES) and about the relative effects on NIS inhibition (Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, Santini F, Crump K, Gibbs J. Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid. 2004;14(12):1012-9), this addition would likely be readily feasible. However, based on the comments of other at the peer review meeting, it is worth noting that because thiocyanate and nitrate exposures are so ubiquitous throughout the population, in effect all of the epidemiological perchlorate data and clinical studies used to obtain model parameters likely were conducted in the setting of similar background exposures to the other NIS inhibitors. Thus, these exposures, although not explicitly discussed, are essentially accounted for in the models.

Excessive, as well as inadequate iodine exposure is associated with adverse effects on thyroid function; models do not appear to account for potential non-linear effects of iodine exposure on thyroid hormone status. This is likely not of concern at the ranges of iodine intakes being studied for most life stages. The exception may be the formula-fed infants, for whom iodine exposures

up to 384 mcg/day are considered. A recent balance study in two month-old infants (A dose-response crossover iodine balance study to determine iodine requirements in early infancy. Dold S, Zimmermann MB, Baumgartner J, Davaz T, Galetti V, Braegger C, Andersson M. Am J Clin Nutr. 2016;104(3):620-8.) found that the iodine requirement at this age is likely about 70 mcg iodine daily, suggesting that levels as high as are found in some U.S. infant formulas are excessive. In the setting of excessively high iodine exposure, perchlorate exposure might actually be beneficial rather than deleterious.

Stephen M. Roberts, Ph.D.

I have no problem with the overall model structure presented and accept the explanations for simplification of some of aspects of the model from previous versions (i.e., reduction in thyroid subcompartments and direct transfer of iodide from mammary plasma to milk). Model structure for the lactating mother, breast-fed infant, and bottle-fed infant appears capable of adequately describing the physiology and kinetics of iodine, thyroid hormones, and perchlorate during these life stages.

For the pregnant woman, modeling is intended to reflect near term pregnancy. However, observations from human studies suggest that risk of adverse neurodevelopmental effects from maternal thyroid deficiency exists throughout pregnancy, and that susceptibility to effects may be highest during early stages of gestation. In view of this, a focus on maternal thyroid effects near term seems to be misplaced. Predictions of maternal thyroid effects from exposure to perchlorate should be extended to earlier time points in pregnancy — ideally to include stages throughout the pregnancy, but minimally to include the first trimester. This may or may not require a change in model structure. During the face-to-face meeting, possible approaches to accomplish this were briefly discussed without a specific recommendation emerging. However, Dr. Pearce offered to make available to the EPA data on iodine, perchlorate, and maternal thyroid hormone status during pregnancy that could be helpful for extending the modeling to different stages of pregnancy.

Joanne F. Rovet, Ph.D.

As above, the model appears to be stronger regarding kinetics of iodide and effects of perchlorate on iodide synthesis than in specifying thyroid-hormone actions and making predictions from the latter set of specifications. The HP-part of the HPT axis is not included nor is the role of deoidinases. The assumption that fT4 is converted equally to fT3 and RT3 is not correct, even though accepted in the Lumen et al. (2013) model. T4 is converted to the active form of T3 via the deiodinadase 2 (D2) enzyme and to the inactive form of reverse T3 by the D3 enzyme. Within the brain, T4 is primary hormone of action. T4 enters the brain at the blood-brain barrier or blood choroid-plexus barrier. T4 is converted to T3 (the active form for gene regulation) within the glia by the D2 enzyme and if in excess, T4 is converted to reverse T3 via D3. The two barriers subserve the development of different brain regions and appear to have different timings of expression. The current model does not consider these different pathways and the specific actions of the different deiodinase enzymes. I believe the current model needs to correct this.

Additionally, free T4 is considered the key hormone but isn't bound hormone (as measured by total T4) the hormone that gains entry into the brain at both barriers?

Finally, the assumption that the P7 infant is equivalent to the neonate is wrong given Vulsma's data showing a steep drop-off in levels of T4 following birth in children with congenital hypothyroidism, thought to reflect the loss of the maternal contribution following parturition. To my knowledge, no evidence exists showing the infant thyroid gains this capacity in the first week of life.

The breast-feeding infant model combined with the lactating mother is to me a single system that is well thought out in showing points of impact of perchlorate, whereas the bottle-feeding infant model fails to realize the impact of perchlorate in the water used to prepare formulas after the infant has graduated from premade formulas (at about 1 month of age). A greater risk of hypothyroxinemia in the lactating than bottle-feeding mother is not known and it is not clear to me why this would represent a sensitive stage when the real issue is the developing brain and its high need for thyroid hormone. Perhaps authors were considering the relationship between hypothyroxinemia and maternal depression in the post-partum. However, to my knowledge, the only person to study this is Victor Pop who examined prenatal hypothyroxinemia and this would be equally present in both types of mothers (i.e., those who do and those who do not breast feed).

Question 1B. Are the physiological and kinetic parameters for iodine, thyroid hormones, and perchlorate for these life stages supported by the published sources for those parameters or data used to identify parameters via calibration? Please identify any critical data gaps and suggest additional data or parameter (values) to these proposed model parameters to address identified gaps.

Hugh A. Barton, Ph.D.

The basis for the model parameters is provided in Tables 4 – 8. In general, it appears the parameters are supported by some information (sometimes visually fitted to the data or the data used directly as table functions).

As also noted in public comments, when the basis of a parameter value is provided as a previous modeling effort (e.g., Fisher et al. 2016, Lumen et al. 2013), this is a secondary source that does not directly identify the supporting information. In several cases additional information is provided, for example the original data source used for the previous modeling. Ideally, this approach would be used for all instances where other models are noted.

In addition, as also noted in public comments, the report states on p 23 that "The review process was halted after it was judged that the objective had been met; i.e., sufficient data for model calibration had been identified." It is not clear what the statement means or how it was decided there were sufficient data. It is also not clear if this means the review of papers from the Dec 2013 search was halted or that further searches of literature were halted. Finally, given the time required to develop the model and prepare documentation, context should be provided for the Dec 2013 date, e.g., initiation of this model development effort, so it does not appear to be

several years out of date for no reason. While it will likely never be possible for the model to catch up with the most current publications, it might be reasonable to carry out searches to determine what new publications were available and whether they essentially augmented existing information (e.g., another cohort of pregnant women with similar measures as previously existed) or potentially provide new information about parameters with assumed values.

Claude Emond, Ph.D.

The physiological parameters are clearly and transparently presented in both model CSL files. When no data were present in the literature to establish the biological relevant, the authors optimized the parameters to fit the biomonitoring human data published. The review draft is very well referenced and helps to build our confidence in using the model.

Dale Hattis, Ph.D.

Briefly, I find several of the comparisons between observations and model predictions unconvincing. For urinary iodide the key discussion appears on page 60:

*"First, model predictions of urinary iodide concentrations for the formula-fed infant were compared with data from Gordon et al. (2014) and Cao et al. (2010). The model simulations were performed based on formula concentrations of iodine reported by Pearce et al. (2004) and perchlorate by Schier et al. (2010). Urinary iodide predictions were not sensitive to perchlorate exposure levels, so for these simulations, the geometric mean perchlorate concentration (0.92 14 µg/L) of all formulas analyzed by Schier et al. (2010) was used for the iodide comparisons (**Figure 4**, top panel). The model-predicted urinary iodide concentration for formula-fed infants with iodine concentrations at the lowest reported value of 108 µg/L by Pearce et al. (2004) were within the range of literature-reported values (**Figure 4**) from Gordon et al. (2014) and from Cao et al. (2010) for both cow milk-based and soy-based formula."*

The figure referred to has an enormous amount of scatter, even with the data points plotted on a logarithmic y-axis. To then say, given this scatter, that "the model-predicted urinary iodide concentrations…were <u>within the range of literature-reported values (Figure 4)</u> really is such a loose standard that it seems hardly meaningful. Minimally, there needs to be some statistical summarization of the comparison data and some specific comparison of the summary data with specific sets of model predictions from models incorporating a range of possible values of key parameters.

The perchlorate comparison is discussed on page 61:

*For perchlorate, data for urinary concentrations were only available for formula-fed infants from Cao et al. (2010). To cover the range of literature-reported perchlorate concentrations, simulations are shown for 0.18 µg/L (minimum measured by Schier et al. (2010)), 0.92 µg/L (geometric mean of values for both soy and cow milk formulas from Schier et al. (2010)), and 4.1 µg/L (maximum value from Pearce et al. (2004), which is higher than the maximum measured by Schier et al. (2010)). Model-predicted concentrations of perchlorate were within the reported values for cow and soy formulas (**Figure 4**, bottom panel)*

The comparison depicted in the bottom panel is also unconvincing, lacking any statistical summarization to help the reader judge whether the comparison supports or refutes the predictions of the model.

Further discussion of the comparison of perchlorate levels appears on page 63:

*The model-predicted urinary perchlorate concentrations were within the range of reported values for birth to 90 days for both formula-fed and breast-fed infants, when perchlorate daily intake was assumed to vary between 0.001 and 1 µg/kg/d (**Figure 6**; data from Leung et al. (2012) and Cao et al. (2010)). Since iodine intake between 75 and 250 µg/day had no effect on predicted urinary perchlorate levels, the iodine intake by the lactating mother was assumed to be 150 µg/day for the perchlorate comparison: a low level within the plausible range for which the model is assumed valid. Since iodine intake has very little effect on predicted perchlorate kinetics, the exact choice of iodine level is not important for this comparison.*

Similarly, the conclusion from Figure 6 that the predicted perchlorate concentrations are "within the range of reported values" is completely unconvincing. What is shown in Figure 6 is a plot of highly scattered observations plotted over a four order of magnitude range with no statistical summarization of the data to allow reasonable juxtaposition of the central tendency and uncertainty range of the observations with corresponding model expectations.

There is a discussion of a comparison of iodide levels on page 64:

*Note: it has been suggested that iodide levels are not stable in breast-milk samples (Dr. Benjamin Blount, CDC, personal communication), which may explain in part why many of the data in **Figure 7** (also see **Figure 17**) are well below the model simulations for 150 and 250 µg/d maternal iodine intake. The predictions for the lowest iodine intake of 75 µg/d are closer to the middle of the range of the data.*

The lack of correspondence of the data points to model predictions is unsettling. And the proffered explanation "that iodide levels are not stable in breast-milk samples" is no help. Instability would be expected to lead to scatter of the data points, but not a systematic bias lowering the data points relative to model expectations. The modelers' response in this case makes no sense.

The overall conclusion of the authors appears on page 67:

*Overall, the model predictions were considered adequate based on the comparison of model 11 simulations to data in **Figure 4-Figure 9***

I disagree. The authors should develop a range of alternative models that would fit these data as well or better based on much more rigorous criteria than that the models produce results "within the range" of the observations presented on multi-order-of magnitude plots. They should then consider and document range of policy-relevant parameter values indicated by running the alternative models with the range of plausible calibrations.

Angela M. Leung, M.D., M.Sc.

Comments regarding calibration parameters:

The models consider published literature to support the calibration parameters for iodine, thyroid hormones, and perchlorate in the lactating mother, breastfed infant, and formula-fed infant.

a. **Lactating mother calibration parameters:**
   - **Iodine in the lactating mother**:
     - Variability of breastmilk iodine concentrations: The parameters for breastmilk iodine concentrations are based on mean values drawn from women examined in relatively small studies. One potentially substantial limitation is that data demonstrating a significant variation of breastmilk iodine concentrations following the ingestion of dietary iodine (Leung et al; PMID 23050787) was not included in the model. In this study of 16 healthy euthyroid lactating women, dietary iodine consumption (600 mcg oral KI) following an overnight fast increased breastmilk iodine concentrations by nearly 8-fold within a few hours, thus illustrating the limitations in the interpretation of random breastmilk iodine content measurements and the challenges of basing the model on mean breastmilk iodine values from relatively small studies. This is hinted at on page 40 lines 5-10 and also on page 6/Figure 6. From the data of Leung et al. (PMID 23050787), the statement on page 40 lines 8-10 is thus inaccurate. Given the impossibility of ascertaining the influence of recent dietary iodine intake in relation to breastmilk iodine values reported in the literature, one can perhaps assume that the lowest and highest range of reported breastmilk iodine values may be that representing all scenarios of dietary iodine intake; this is important to note in the model report as a limitation and caveat to the model. Incidentally, the median (IQR) *fasting* breastmilk iodine concentration in this study was 45.5 mcg/L (34.5-169 mcg/L), which is comparable to the Leung 2012 study used for calibration of the current model.
     - Mean breastmilk iodine concentrations: Recognizing that in the absence of a larger study assessing the impact of dietary iodine on breastmilk iodine concentrations, the model can only rely on mean breastmilk iodine concentrations taken from random collections as much as possible. Other U.S. data on breastmilk iodine concentrations have been reported in 57 healthy women (Pearce et al.; PMID 17311853) that are not included and can be used to improve the calibration of the model. This study by Pearce et al. also reports the perchlorate content in the subjects' breastmilk; urinary iodine and perchlorate concentrations; and 17 brands of infant formula that subjects reported use of during pregnancy.
     - Breastfeeding exclusivity: An important caveat is that many of the studies in the literature did not examine women who were exclusively breastfeeding, and thus the iodine nutrition provided to their infants was derived from a combination of breastmilk and formula sources. Calibration of the model to the published ranges of iodine and concentrations in breastmilk, maternal urine, and infant urine, and for infant serum thyroid hormones may thus be

inaccurate.

- **Thyroid hormones in the lactating mother:**
  - TT4 reference range:
  1. The *pregnancy* model is based on TT4 reference ranges as reported in 6 studies (page 20, lines 5-7). The *lactation* model is based on serum FT4 concentrations from only 48 total women from two NHANES cohorts (page 20, lines 16-22). The small n used for the lactation model is concerning for its accuracy. Also, it should be stated clearly in the text that the following influence serum thyroid hormone concentrations during pregnancy and lactation: preexisting thyroid disease and/or use of thyroid hormone replacement or antithyroidal medications, positive serum thyroid autoantibodies, hyperemesis gravidarum, trophoblastic disease, and preeclampsia, and whether these were assessed in any of the quoted studies from which the models are based.
  2. There are several potential concerns regarding the adaptation of the human pregnancy thyroid physiology model for use in the lactation model. In general, thyroid hormone requirements are increased in pregnancy, compared to lactation, due to the following factors: 1) It is well-known that thyroid hormone requirements and thus, thyroid hormone production, increases by approximately 2-fold from the beginning of pregnancy to mid-gestation, due primarily to the increases in thyroid binding globulin (TBG) that is seen with increased estrogen levels during pregnancy (Glinoer; PMID 9183570). The thyroid hormone requirements decrease back to pre-pregnancy levels following delivery. 2) There are rises in serum FT4 concentrations, particularly during the first trimester, due to the rise of beta-HCG during this timeframe. 3) There is an increase in plasma volume during pregnancy that corresponds to increased thyroid hormone requirements during pregnancy. 4) There is an acceleration of serum T3 and T4 degradation during pregnancy, due to the effect of abundant type 3 deiodinase expression and activity in the placenta and uterine and fetal tissues. In summary, for these reasons, the extrapolation of serum thyroid hormone levels during pregnancy for use in lactation is not ideal (page 14 lines 11-12). For the lactation model, non-pregnant serum thyroid hormone concentrations would be more accurate.
- **Perchlorate in the lactating mother:**
  - The report states that the details of the EPA perchlorate and radioiodide PBPK models for the lactating mother are referenced in McLanahan et al. 2014 and U.S. EPA 2009. The current model was simplified from the previous PBPK models according to the following changes: the thyroidal subcompartments for perchlorate was reduced to plasma and tissue (similar to iodine), and perchlorate transport in mammary cells is shown to occur as a one-step process from plasma to breastmilk. Key perchlorate PBPK model parameter changes resulting from these revisions are summarized on pages 44-45 of the report. My expertise is not in this area, and I am unable to comment further regarding this question.

b. Breastfed infant calibration parameters:

- **Iodine, thyroid hormones, and perchlorate in the breastfed infant**:
  - Leung et al. (2012) publication: It should be noted that the report by Leung et al. (2012) used in calibration of the model included both exclusively breastfed infants (35% of the sample size), as well as those who also partially consumed infant formula (65% of the sample size). This clarification is missing from Table 2 and in the corresponding text; it is a significant limitation of the current model, as it assumes that all data was obtained from exclusively breastfed infants.
  - Cao et al. (2010) publication: Similarly, this report included both breastfed infants (46% of the sample size) and formula-fed infants (54% of the sample size), as noted in Table 2. The use of urinary iodine and perchlorate concentrations from this study for model calibration thus is not completely accurate when assuming they are resulting from exclusive breastfeeding or exclusive formula-feeding.
  - Colostrum iodine concentrations: The report outlines the reasons for not analyzing neonates between days 0-7 of postnatal life, primarily the physiologic surge of TSH levels in the immediate postpartum period, which is a valid argument. However, there are data examining perchlorate and iodine levels in colostrum (form of breastmilk beginning in late pregnancy and continuing in the first few days after delivery) and in the urine of postpartum women (Leung et al; PMID: 18616704). These data may be helpful to include in the report to further strengthen the current model's relationships between perchlorate exposure and breastmilk iodine levels in lactating women; the relationship does not have to be included in the model, but can be used to assess trends of the impact of perchlorate exposure when comparing neonates <7 days to those >7 days of newborn life. A study has reported that the estimated iodine intake from breastmilk and infant formula during this early period, days 1-2 after birth, are 20.0 ± 11.9 mcg/day and 13.0 ± 3.3 mcg/day, respectively (Gokmen IG et al; PMID 7661341).
  - Maternal 24-hour urinary iodine excretion: There are data reporting that estimated urinary iodine 24-hour excretion rates in the mother are a better reflection of iodine supply than perhaps breastmilk iodine to the breastfed infant (Andersen SL et al.; PMID 2419933) for the reasons delineated in response #1Ba (*calibration parameters for breastmilk iodine in the lactating mother*). It is interesting to note that these data by Andersen et al. also demonstrate that breastmilk iodine concentrations are not correlated with maternal fluid intake.

c. Formula-fed infant calibration parameters:

- **Iodine in the formula-fed infant**: The model is built on data by Pearce et al. (2004) that reported the iodine content of eight brands of U.S. infant formula. Given this limited data, it may be worthwhile to also consider additional available data:
  - There is an additional study of U.S. brands of infant formula reporting a detectable range of perchlorate in all 17 products tested (range, 0.22-4.1 mcg/L) (Pearce EN et al; PMID 17311853).

  - Although it is a Spanish study, the measured iodine content of 27 brands of infant formula in Spain (Fernandez-Sanchez LM et al; PMID 18039487) report a mean iodine concentration of 53.5 ± 19.5 mcg per 100g sample.
  - Additional data regarding the iodine content of infant formulae are also described in the Comprehensive Handbook of Iodine 2009, which should be considered and referenced.
- **Urinary iodine, urinary perchlorate, and serum thyroid hormones in the formula-fed infant:**
  - Leung et al. (2012) publication: It should be noted that the report by Leung et al. (2012) used in calibration of the model included both exclusively breastfed infants (35% of the sample size), as well as those who also partially consumed infant formula (65% of the sample size). This clarification is missing from Table 2 and in the corresponding text; it is a significant limitation of the current model, as it assumes that all data was obtained from exclusively breastfed infants.
  - Cao et al. (2010) publication: Similarly, this report included both breastfed infants (46% of the sample size) and formula-fed infants (54% of the sample size), as noted in Table 2. The use of urinary iodine and perchlorate concentrations from this study for model calibration thus is not completely accurate when assuming they are resulting from exclusive breastfeeding or exclusive formula-feeding.

Characterizing TH regulation in pregnancy

The 2016 American Thyroid Association pregnancy and postpartum guidelines provide the relevant references pertaining to the beginning of pregnancy, with a comprehensive summary of the global literature on this listed in Table 4 (Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017 Mar;27(3):315-389. doi: 10.1089/thy.2016.0457.)

In addition, I agree with Dr. Pearce's recommendations for the publications listed in the pre-meeting comments (Question 3B), many of which overlap in the 2016 ATA pregnancy and postpartum guidelines stated above.

The U.S. National Health and Nutrition Examination Survey datasets (multiple sets since the 1970s) are the most relevant in reporting population-level reference ranges for serum TSH and thyroid hormone concentrations. These data are stratified by gender and age group and freely accessibly at https://www.cdc.gov/nchs/nhanes/index.htm.

One seminal publication (Surks MI and Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007 Dec;92(12):4575-82) is a recent summary of these data among both disease-free individuals (no known thyroid disease or use of thyroid-related medications) and the reference population (non-pregnant and thyroid antibody negativity).

Michael H. Lumpkin, Ph.D., DABT

The report describes in detail the selection of data that serve as the basis of model parameter values for the various life stages. This includes the consideration of data published or made available since publication of the respective Lumen/Fisher/Clewell/McLanahan models. The data utilized to populate parameter values are adequately justified in the report. I am not aware of additional data that should be considered or preferentially utilized in the place of data described in the report.

Elizabeth N. Pearce, M.D., M.Sc.

Free T4 assays, as noted in the text, are poorly concordant with each other in pregnancy and some assays lose the expected inverse relationship with serum TSH values (Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, Braverman LE, Goodwin TM. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol. 2009;200(3):260.e1-6.). It is generally recommended that normal thyroid function reference ranges be assay-specific, and that they should be defined in populations of individuals with no known history of thyroid disease, with adequate iodine intakes, and with negative thyroperoxidase (TPO antibodies). Among the studies used to derive free T4 reference values for the pregnancy BBDR models, the studies by Yan, Sticker et al. clearly met those criteria. The paper by Gong and Hoffman excluded TPO positive women; the sample was from Toronto, which likely means it was iodine sufficient. Similarly, the study by Wang et al. did not specify the study population's iodine status, although women were TPO Ab negative. In the study by Khalid et al., TPO antibody positivity was excluded and although urinary iodine was not ascertained, the study population, from Ireland, was most likely mildly to moderately iodine deficient. Additional data which could inform the definition of normal free T4 values in pregnancy are listed below under section 3A.

Hypothyroxinemia in lactating women, as noted above, is not currently considered a clinical adverse outcome, and thus there is essentially no literature on this entity. After the first 2-3 weeks postpartum (when thyroid hormone levels are equilibrating after the changes of pregnancy), there is no reason to believe that reference intervals for free T4 should be any different in lactating women than they are for non-pregnant, non-lactating women. Unlike in pregnancy, there is not a strong hormonal driver for increased thyroid hormone production or metabolism (oxytocin and prolactin, the major breastfeeding hormones, should not affect thyroid hormone production or metabolism). The amount of thyroid hormone secreted in breast milk is negligible (van Wassenaer AG, Stulp MR, Valianpour F, Tamminga P, Ris Stalpers C, de Randamie JS, van Beusekom C, de Vijlder JJ 2002 The quantity of thyroid hormone in human milk is too low to influence plasma thyroid hormone levels in the very preterm infant. Clin Endocrinol (Oxf) 56(5):621-627). Therefore, it should be possible to use the broader dataset for TPO negative, age-matched, non-pregnant women from NHANES as well as data from other published sources to inform reference ranges for free T4 in the women who are lactating. The model currently uses data from only 39 lactating women from NHANES 2007-2008 and 2009-2010; this data set is very small and may include women with thyroid autoimmunity. Up to 10% of women experience postpartum thyroiditis. Postpartum thyroiditis is an autoimmune condition which presents in the first 6-12 months following delivery in which there is initially inflammation of the thyroid gland allowing pre-formed thyroid hormones to leak into the circulation (causing low TSH and high free T4 and T3). This is often followed by a period of

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hypothyroidism as the pre-formed thyroid hormone is depleted and the thyroid has not healed sufficiently to produce adequate thyroid hormone. Usually this ultimately resolves without intervention. Because this is a process in which circulating thyroid hormone levels would not be influenced by either iodine or perchlorate exposure, it is important to exclude these women from data sets used for model calibrations.

Decreasing excretion of urinary iodine in seven women over time was noted by Aboul-Khair et al. in data used to inform urinary iodine values for lactating women in the BBDR model. I am not able to access this paper, but have concerns about both the very small sample size and about what was known about the underlying iodine sufficiency of the women studied. Trends over the course of the first 90 days postpartum might be quite variable depending on ongoing iodine intake and presence or absence of adequate intrathyroidal iodine stores.

Table 6: The fractional kidney blood flow in third trimester women is assumed to be the same as for lactation. However, glomerular filtration rates and renal plasma flow are thought to be substantially increased in pregnancy (Dunlop W. Serial changes in renal hemodynamics during normal human pregnancy. Br J Obstet Gynaecol. 1981;88(1):1–9.).

Table 8: The free fraction of total T4 was estimated at 9×10^{-5} whereas it is estimated as 1×10^{-4} in lactating women. These fractions do not appear to fit with the knowledge that thyroxine binding globulin concentrations are increased twofold in pregnancy (Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab. 1987;65(4):689.).

Page 43: it is noted with respect to the model for lactating women that "the clearance rate for metabolism or deiodination of T4 was set equal to the value for pregnant women.": This is likely inappropriate; given the high levels of type 3 deiodinase found in the placenta, the rate of thyroid hormone metabolism would be expected to be higher in pregnancy than in lactation. Page App-12: It its stated that "while there was uncertainty regarding the urinary clearance of perchlorate in lactating women vs. non-lactating women, there were no data or known biological reasons to expect it to be significantly different": this assumption is reasonable. However, on page App-17 it is noted that "maternal clearance of perchlorate is assumed to be lower during pregnancy": it seems more likely that the opposite would be true, given increased glomerular filtration rates in pregnant women.

Stephen M. Roberts, Ph.D.

Citations are provided for physiological and kinetic parameters taken from published sources. There are numerous data gaps for physiological and kinetic parameters, and these are discussed in the section on BBDR Model Development and Parameterization (beginning on page 22) in the context of the rationale for selection of various specific values. Drs. Leung and Pearce had several important pre-meeting and face-to-face meeting comments on the lactating mother, breast-fed infant, and formula-fed infant calibration parameters. Also, as noted under General Impressions, it will be important to extend modeling in the pregnant woman to include various, and particularly early, gestational stages. Data with which to do this are limited, but Dr. Pearce offered the availability of data from her research that may be useful for this purpose.

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Joanne F. Rovet, Ph.D.

The SAB-PAP report stressed the need to look at pregnancy and fetal thyroid function as key sensitive stages. Current authors maintain they did not include these stages as the relevant data for modelling are not available. This is surprising as much data exist on maternal thyroid levels and fetal data are available in the work of Thorpe-Beeston and on preterm infants (e.g., see work of Hume and Williams). Data too from the Rotterdam, Chinese, and Scandinavian cohorts could likely fill in a number of gaps. Authors need to see the paper by Peter Taylor et al. (2014) on perchlorate in pregnancy and offspring IQ. Authors do extrapolate results to pregnant women and fetus, but I am not sure how this is done and when in pregnancy or fetal development this represents.

Question 1C. While the model predicts the dose-response for fetal thyroid hormones, a reference range for the fetus was not identified. Are there additional data, parameters, or (sub)models available that might be useful for evaluating fetal effects? If not, can the predictions for thyroid hormone changes in the pregnant mother be used as a measure of potential fetal effects?

Hugh A. Barton, Ph.D.

As noted above, the current pregnancy model is limited to term and needs to be extended to address earlier pregnancy given the available data linking maternal thyroid hormone levels with neurodevelopmental outcomes. One peer reviewer noted that there are iodine supplementation studies which indicate that supplementation during the second/third trimesters do not appear to alter the impacts of first trimester iodine status. This suggests that while ultimate effects may reflect cumulative thyroid status throughout pregnancy, the first trimester would be an essential period to include in the model. That modeling would focus on maternal hormonal status, so modeling fetal levels (which are entirely obtained from the mother in the first trimester) and defining a reference range may not even been necessary.

Claude Emond, Ph.D.

This limitation regarding the reference range for the fetus might be an issue. It is discussed in the current draft review. As far as I know, there is no another reference that the authors might have forgotten to include in the PBPK model that suggests the possibility to describe the interaction of the fetus with the T3 and T4 hormones during gestation. This might be an issue; therefore, I believe that the reference range for the fetus should be part of the recommendation to generate data. T3 and T4 are highly important hormones in general development, including the brain. A lower concentration of fT4 and T4 resulting from perchlorate disruption would be an important issue to resolve.

Dale Hattis, Ph.D.

The emphasis on a "reference range" for hormone levels is, I think, a mistake. The implication is that values within the reference range carry no risk of harm and concern for adverse effects only arises if an individual who would ordinarily be in the reference range is moved by an exposure outside of the range. In fact, the most recently published analysis of data from a large

prospective study (Korevaar et al. 2016) suggests that there is an optimum level of maternal free thyroxine for neurodevelopment, and a continuous form for changes in later IQ with both upward and downward departures from this optimum:

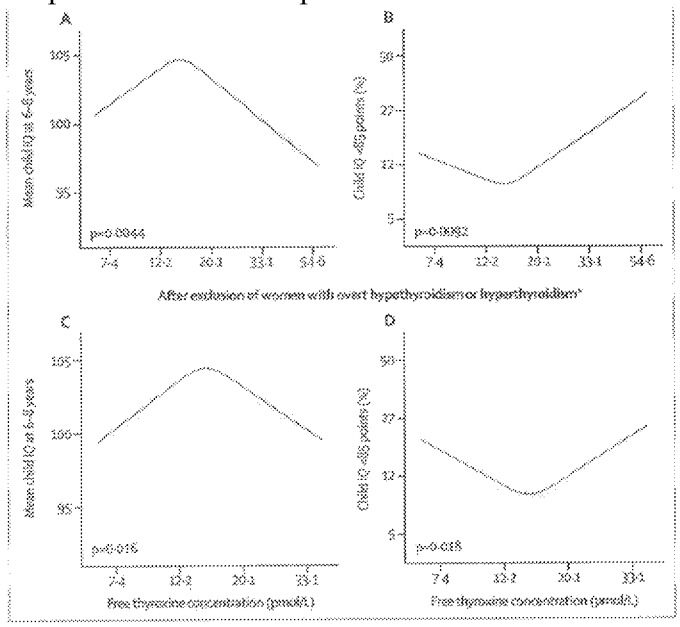

Figure 2: **Association between maternal free thyroxine and offspring IQ**
(A, C) Association between maternal free thyroxine concentrations during pregnancy and child IQ as predicted mean and 95% CI in the whole population (A) and after the exclusion of women with overt thyroid disease (C). (B, D) Association of maternal free thyroxine levels during pregnancy and the risk of child IQ below 85 as predicted back-transformed log odds with 95% CI in the whole population (B) and after the exclusion of women with overt thyroid disease (D). Scales for the x-axis might differ between the upper and lower graphs because of exclusions of women with overt, but not subclinical, disease entities. Appendix p 5 provides effect estimates from standard linear regression models. IQ=intelligence quotient. *Overt hypothyroidism and hyperthyroidism are defined as the biochemical diagnosis made during pregnancy, based on the central 95% reference range, as advocated in international guidelines.

Source: Korevaar et al. (2016)

It must be noted that these plots have logarithmic axes for the independent variable, free thyroxine concentration. This means that if the relationships were plotted on linear axes, the lines to the left of the optima would appear much steeper than the lines to the right of the optima. The net effects need to take into account both the baseline population distribution and the net changes expected both to the left and the right of the optima.

Angela M. Leung, M.D., M.Sc.

Comments regarding fetal thyroid hormone concentrations:

The model's primary outcome is hypothyroxinemia as mediated by iodine status. However, hypothyroxinemia in the fetus was not able to be estimated by the current model, due to the inavailability of "in utero" fetal FT4 reference ranges in the current literature.

The fetus is one of the population subgroups who may be particularly susceptible to perchlorate exposure, given its biologic action on thyroidal iodine availability and therefore thyroid hormone production and brain development. Brain development in utero begins as early as 5 gestational weeks (Berbel et al; PMID 17962037). As the fetal thyroid gland is not functional until approximately 18-20 gestational weeks (Smallridge RC et al; PMID 11397821), normal brain dependent in the fetus is completely reliant on maternal transplacental passage of adequate

thyroid hormone. However, even at 5 gestational weeks, the fetal thyroid is immature and thus continues to depend on maternal thyroid hormone throughout the rest of gestation, such that up to 50% of fetal T4 at delivery is that which is derived from the mother. As such, predictions of maternal thyroid hormone changes during pregnancy can serve as only a partial measure of thyroid hormone status in the fetus.

Michael H. Lumpkin, Ph.D., DABT

I am not aware of additional data, parameters, or submodels available that might be useful for evaluating fetal effects independent of the maternal effects. The varied and significant changes in fetal thyroid hormone changes in the first days after birth may make the choice of a gestation week 40 fetal reference range moot.

Elizabeth N. Pearce, M.D., M.Sc.

Fetal thyroid function cannot be directly measured without risk to the pregnancy. Therefore, there are few human studies examining fetal thyroid function (Costa A, Arisio R, Benedetto C, Bertino E, Fabris C, Giraudi G, Marozio L, Maulà V, Pagliano M, Testori O, et al. Thyroid hormones in tissues from human embryos and fetuses.J Endocrinol Invest. 1991;14(7):559-68). I think it is entirely reasonable to use maternal thyroid function as a proxy, especially given that data for adverse child developmental effects are known with respect to maternal, but not fetal, hypothyroxinemia. As noted above, however, I think it is important to extend the BBDR model to cover the first and second trimesters of pregnancy because there are currently no data for associations between third-trimester maternal hypothyroxinemia and adverse developmental outcomes.

A recent study from the Generation R Cohort (Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol. 2016;4(1):35-43) is the only one to date to examine correlations between maternal free T4 in early pregnancy and child IQ. The only study thus far to directly examine effects of maternal perchlorate exposure on child IQ is: Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice R, Channon S, Braverman LE, Dayan CM, Lazarus JH, Pearce EN. Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the Controlled Antenatal Thyroid Study. J Clin Endocrinol Metab. 2014;99(11):4291-8. In this analysis we found that in an iodine-deficient cohort maternal urinary perchlorate levels in the highest 10% increased the odds of offspring IQ at age 3 being in the lowest 10%, with a greater adverse impact observed for verbal IQ than for performance IQ. Maternal levothyroxine therapy did not appear to reduce the negative impact of perchlorate on offspring IQ. These data require confirmation in larger cohorts, and are perplexing because previously no association between maternal thyroid function and maternal urinary perchlorate concentrations were observed in this cohort (Pearce EN, Lazarus JH, Smyth PP, He X, Dall'amico D, Parkes AB, Burns R, Smith DF, Maina A, Bestwick JP, Jooman M, Leung AM, Braverman LE. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. J Clin Endocrinol Metab. 2010;95(7):3207-15).

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Stephen M. Roberts, Ph.D.

Concern for the fetus as a sensitive life stage with respect to perchlorate effects is based in large part on observations of neurodevelopmental deficits among offspring of women who were thyroid deficient during pregnancy. The SAB Perchlorate Advisory Panel recommended that the EPA consider as a sensitive population the fetuses of hypothyroxinemic pregnant women; hence the need to develop a model capable of predicting the potential influence of perchlorate on hypothyroxinemia in pregnant women. Prediction of perchlorate effects on fetal thyroid hormones is not required in order to derive a perchlorate limit protective of neurodevelopmental effects from exposure during gestation. In fact, even if fetal thyroid levels could be confidently modeled, there is no means to interpret them, i.e., there are no data to know what human fetal thyroid hormone levels are associated with neurodevelopmental effects. With the current state of knowledge, both attempts to estimate fetal thyroid changes and to quantify neurodevelopmental effects as a result of those changes would be highly uncertain.

Joanne F. Rovet, Ph.D.

See above. As a writer of the SAB-PAP report, I find this lack of data very disappointing. Yes, thyroid hormone changes in the pregnant mother can be used as a measure of potential fetal effects, especially in early pregnancy when the mother is the sole source of thyroid hormone for the fetal brain – and mothers' levels are known. Also, data from studies of preterm infants by the Scottish group under Hume and Williams can indicate thyroid-hormone capacity of the fetus in the third trimester.

Question 2. Modifications to existing models: EPA has modified one parameter in the 2013 Lumen et al. model: KM_TPNG, the Michaelis-Menten constant for the sodium-iodide symporter for perchlorate based on Schlosser (2016), and a second key parameter in the 2009 USEPA/2007 Clewell et al. PBPK models: VMAXC_MKP, the maximal velocity for perchlorate transfer to breast milk from those components in the USEPA 2009 models. These two parameters affect perchlorate transport from the mammary plasma to breast milk (VMAXC_MKP) and the strength with which perchlorate inhibits iodine transport by the sodium-iodine symporter (KM_TPNG). Detailed information on the assumptions and data considered in making these changes are provided in the report appendices. Are the changes scientifically supported and reasonably estimated?

Hugh A. Barton, Ph.D.

The change in Km value published in Schlosser (2016) is a reasonable scientifically supported reanalysis of the data used to establish that value. The logic presented of how the previous analysis had obtained the original Km value and the approach looking across the range of the available data is appropriate. Assuming this value to be life stage independent is an assumption, but a reasonable one absent other information.

It is more challenging to evaluate the change in VMAXC_MKP as the data are fairly scattered and addressing the range of perchlorate in milk versus urinary excretion required adjustments to other parameters, QMWB, mammary blood flow and PAMKC-P, passive diffusion of

perchlorate. The approach appears reasonable, though absent working with the model directly it is difficult to have a clear perspective.

Claude Emond, Ph.D.

Lines 2 through 8, page 45

- The affinity constant (Km) for binding of perchlorate to the sodium-iodide symporter (NIS) (KM_TPNG) was reduced from 1.6×10^5 ng/L to 6×10^4 ng/L (Schlosser, 2016) because the in vitro data were reanalyzed (Kosugi et al., 1996). The same report suggests that making this modification results in a better prediction of the radioiodine uptake inhibition data from Greer et al. (2002) for the dose of 100 µg/kg/d than the simulation observed with the previous Km.

Lines 17 through 23, page 45

- Vmax for perchlorate transport from the mammary plasma to the milk call (VMAXC_MKP) also had a significant impact on model predictions. The authors were precise because they increased this value from the original model by a factor of 2.24; however, in the code file, they referred to this change because of "Schlosser paper (2016)". It should be referenced on page 45, line 23.
- As mentioned by the authors of this report, two parameters (i.e., VMAXC_MKP and KM_TPNG) are very sensitive. Rather than just mentioning it, the authors should further discuss these two parameters in the report. In addition, a sensitivity analysis of these two values should be included in the Sensitivity Analysis section, but they are not.

Dale Hattis, Ph.D.

First, given that these parameters are important determinants of the ultimate behavior of the pharmacokinetic model, it is a serious mistake to represent them as point estimates without estimates of either uncertainty nor variability distributions and analyses of the implications of these for policy-relevant outcomes.

The affinity of the symporter for iodide (KM_TPNG) appears to have been derived by picking a value and subjectively evaluating fit to the Greer data (App-11, Figure B-5). The new value clearly provides a better fit than the older value which was apparently based on fitting only the lowest point in the Greer data set. However, it seems to me that the fit could and should be further improved by a formal minimization of the statistically weighted departure of the model predictions from the data. Generally, the weighting for the data points should be based on the inverse of the uncertainty variance in either linear or log space depending on whether the sources of the errors in the data appear to be combine in an additive or a multiplicative way.

Angela M. Leung, M.D., M.Sc.

Comments regarding modifications to existing models:

The modifications as summarized on pages 44-45 and Appendix B were reviewed. The two main modifications were the reduction of the affinity constant (Km) for the binding of perchlorate to NIS and the increased Vmax value for the transport of perchlorate from mammary

plasma to breastmilk. This technical modeling aspects of this report are not my area of expertise, and thus I cannot comment on whether these are scientifically supported and/or reasonably estimated.

Michael H. Lumpkin, Ph.D., DABT

The justifications for modifying the NIS Michaelis-Menton constant (KM-TPNG) downward and adjusting blood-to-milk perchlorate transport velocity (VMAXC_MKP) using more robust data are sufficiently supported in the model report by the available data. Given the model structure changes required to align the perchlorate PBPK and iodine BBDR models, the need to revisit the model's fidelity to replicate the Greer et al. data was warranted. EPA noted that the non-pregnant female ("adult") model does not adequately replicate the RAUI behavior reported by Greer et al. for perchlorate doses above the RfD POD of 7 µg/kg/day. The strategy to begin by comparing the resulting Vmax values obtained for the older models using graphical methods to transform the data to linear relationships (as was done by Kosugi et al. [1996]) with novel fitting of the Kosugi et al. (1996) *in vitro* data using modern non-linear fitting techniques makes sense. The newly fitted Vmax value resulted in far better concordance of the model-predicted RAUI for non-pregnant women with the Greer et al. data. The EPA approach to testing the performance of the lactating mother model with the revised KM-TPNG value was also reasonable, utilizing gestation week 38 iodide burdens as the initial conditions to simulate the Greer et al. experiment.

The use of the newer and more robust breast milk/urinary perchlorate concentration data of Kirk et al. (2013), compared to that of Tellez et al. (2005) to calibrate the rate of transport of perchlorate and iodine into breast milk was adequately justified din the report. EPA showed that the Kirk data provide more detailed and statistically powerful information with which to explore the relationship between perchlorate elimination to breast milk or urine in the lactating mother. The use of the multiplicative factor vmult to scale mammary blood flow with mammary Vmax for perchlorate adequately captured the extreme values of mammary elimination of perchlorate in the Kirk et al. study population.

Elizabeth N. Pearce, M.D., M.Sc.

The decision to eliminate the thyroid lumen as a separate model compartment seems reasonable, as does the decision to simplify the model to allow transport directly from mammary plasma to the breast milk. I also agree that it is reasonable to assume that the Km for iodine and for perchlorate are the same for NIS in the breast as they are for NIS in other tissues. It is reasonable to assume that the perchlorate urinary clearance will be the same in lactating women as in non-pregnant, non-lactating women (but not that it will be the same as in pregnant women, in whom glomerular filtration rates are increased).

The revised $Km_{NIS,ClO4}$ based on the re-analysis of the Kosugi (1996) paper is based on reasonable assumptions, however, given that the original Kosugi data were not actually available, the calibration of the model against existing datasets (see below) is particularly critical.

Stephen M. Roberts, Ph.D.

Explanations for the changes in parameters VMAXC_MKP and KM_TPNG are provided in Appendix B. The rationale and procedure for the change in KM_TPNG is reasonable and scientifically supported. During the face-to-face meeting, some panel members indicated that they had read the Schlosser (2016) paper, and that it was helpful in understanding the justification and procedure for changing this variable. The EPA should consider bringing additional information from the Schlosser paper into the report to further clarify the basis for the KM_TPNG change. The narrative describing the rationale and procedure for the change in VMAXC_MKP is more difficult to follow. Without additional explanation, I am unable to determine whether this change is scientifically supported and reasonably estimated.

Joanne F. Rovet, Ph.D.

These seem reasonable to me.

Question 3. Model calibration and sensitivity analysis: Please address the strengths and limitations of the model calibration process and the strengths and limitations of the data used for model calibration and evaluation. Identify any additional literature, data, or peer reviewed models that EPA should consider to address identified limitations.

Hugh A. Barton, Ph.D.

The strategy described for calibrating the formula fed infant first followed by the breast-fed infant and nursing mother is a logical one since the formula fed infant would be independent of the maternal parameters after birth.

Claude Emond, Ph.D.

No comment here.

Dale Hattis, Ph.D.

The fitting described in Appendix B appears to have been done without formal statistical optimization one parameter at a time, sometimes (as in the case of the Vmax value for the symporter transfer) accompanied by adjustment of another parameter, in that case the " permeability-area constant for diffusional transfer" (App 15, line 16). On the following page further individual ad hoc adjustments are described to mammary blood flow. When the values of multiple parameters are being tweaked and fits evaluated against multiple and diverse sets of observational data, I have found it to be helpful to have a much more formal search process with simultaneous variation of all the adjustable parameters and evaluation of overall fit considering the inverse-variance weighted departures of the model predictions from all the observational data sets being considered. Otherwise, the repeated adjustment of all the model parameters becomes just too complicated for me to trust my subjective judgment of fit.

Angela M. Leung, M.D., M.Sc.

Comments regarding the model calibration process and sensitivity analysis:

a. Model calibration
   - Calibration has been attempted to be done utilizing the available data from the literature regarding iodine, perchlorate, and thyroid hormone measurements in lactating women and infants. However, some of the data are misinterpreted (see my responses to Question 1B) or missing; thus, the model contains some calibration parameters that may be inexact, particularly for breastmilk and urinary iodine concentrations.
   - The statements regarding the instability of iodine levels in breastmilk on page 64 line 9 and page 82 lines 10-13 are likely misinterpretations of the personal communications with Dr. Blount, as iodine is an extremely stable element and their concentrations are unlikely to change within such short timeframes.

b. Model sensitivity analysis

Please see my responses below in Question 3B.

Michael H. Lumpkin, Ph.D., DABT

Strengths of the data set utilized for model calibration and evaluation include the use of data from the actual human population (including the most sensitive sub-population) for which health risks a will be evaluated. Further, the data for iodide, perchlorate, and thyroid hormone levels that was used for model evaluation are in the approximate concentration space (0-20 µg/kg/d perchlorate; 9-16 pM serum fT4) for which the model was intended *a priori*. The obvious limitation of the calibration data set is the lack of known exposure levels resulting in the literature and NHANES-reported levels of iodide and perchlorate in blood, urine and breast milk. If the model were to include the 1st trimester fetal life stage, then epidemiological data from several cohorts of pregnant women exposed to regionally-known perchlorate levels in drinking water (some at high levels, relative to the perchlorate dose range explored in the BBDR model report) can be utilized in the calibration process and help to inform whether the perchlorate dose-response can be adequately predicted in the absence of modeling TSH feedback mechanisms.

Elizabeth N. Pearce, M.D., M.Sc.

Strengths of the model calibrations and sensitivity analysis process include attention to calibrating the model against representative data for each life stage, and testing over a range of assumed iodine and perchlorate exposures.

It was reasonable to exclude neonatal data from the first 7 days of life in model calibrations due to the difficulty of dealing with effects of the neonatal TSH surge.

The primary weaknesses of the model calibration process was the limited nature of the datasets against which model was validated. Suggestions for additional studies are below (3A).

Leung et al. (2012) was used as the primary data source for deriving NIS-mediated uptake of iodine into breast milk. It is notable that breast milk iodine concentrations among the women in

that study were extremely variable, and that the number of exclusively breastfed infants was quite small. As we concluded in that study, timing of breast milk sampling is likely one factor which explains some of the variability in measured samples; we have shown that breast milk content peaks at 6 hours after a mother ingests an iodine load. The model assumes a constant rate of iodine excretion into breast milk, which is not the case, and may complicate efforts at model calibration.

Stephen M. Roberts, Ph.D.

The obvious strength of the model calibration process is that much of the data used for this purpose comes from studies of humans. There are, however, several limitations and weaknesses in these data. Specific examples are provided in comments by Drs. Pearce and Leung. A general weakness is the limited nature of data available — few studies and small numbers of subjects. This weakness is compounded by the use primarily of data from studies published in or before 2013. Dr. Pearce, in her preliminary comments, provided several more recent studies the EPA should consider, and Drs. Pearce and Leung offered during the face-to-face meeting access to some of their research data that could be useful for model calibration and evaluation.

Joanne F. Rovet, Ph.D.

I am not too familiar with this literature but it seems to me that most of the papers I could find are cited or authored by members of the modeling team. This is definitely an area of strength of the modelers.

Question 3A. Specifically, is the model calibration and evaluation adequately compared with what is reported in the literature for iodine and perchlorate concentrations in urine, and breast milk and thyroid hormone plasma concentrations under different iodine intake and perchlorate exposure scenarios? Please identify additional studies that would support model calibration that strengthen the proposed model.

Hugh A. Barton, Ph.D.

The model simulations shown in Figures 4 – 9 seem reasonable with some of the discrepancies as described in the report. A challenge for this calibration is that there are other factors contributing to the observed population variability that are not incorporated into the model (e.g., variability in PK determinants like NIS for iodide and perchlorate handling, variability in thyroid hormone production and clearance, variability of intake for other NIS inhibitors potentially in diet or other sources). However, trying to add the variability into the model would only make sense if it appears to reasonably capture the average behaviors. Like any biologically based model attempting to simulate data across a wide range of endpoints from studies with different designs, some simulations are better than others. It is challenging to understand how well the available data determine the parameters that were fitted without doing a sensitivity analysis for each endpoint and study design. The variability may be important in that several studies did not find correlations among iodine and/or perchlorate levels and thyroid hormone levels (in either urine or plasma for different study designs) suggesting that other factors were contributing. The model has a deterministic description of perchlorate inhibition of iodine transport and the impact on thyroid hormone levels, so this could be perceived to be at odds with

the data. It seems plausible, however, that there are other factors (some noted above) contributing to the variability that obscure relationships among iodine, perchlorate, and thyroid hormone absent exact accounting for co-variates or other approaches for population variability. This will make it challenging to use the modeling to establish a health protective level challenging and maintaining the credibility of the analysis. As noted, the easy answer, also suggested in some of the public comments, is to further expand the model to include these sources of variability, but that may not be so easy to do and demonstrate that the results are more strongly supported than the current analyses. This is an area that would benefit from at least qualitative discussion and clear acknowledgement of current limitations of the modeling, though there are not necessarily easy alternative approaches to apply that have fewer limitations.

Claude Emond, Ph.D.

I did not find any additional literature that may further support the authors' research regarding this model. I believe this report contains the major publications available.

Dale Hattis, Ph.D.

I think not. There needs to be a much more formal process of comparison of model predictions and observed data. Uncertainties in the data should be modeled and expressed as confidence limits, and summarized for comparison with model predictions.

Angela M. Leung, M.D., M.Sc.

Comments regarding model calibration and evaluation under different iodine and perchlorate scenarios:

Figures 4-9 report the model calibration results compared to data in the literature for iodine and perchlorate concentrations in urine and breastmilk and of serum thyroid hormone concentrations under different iodine intake and perchlorate exposure scenarios. As noted in my responses to Question 1B, there are some additional studies that should be reexamined and/or included to strengthen the calibration. Some specific comments are as follows:

- Figure 4 (Urinary iodine and perchlorate for formula-fed infants): It is reassuring that the model-predicted urinary iodine concentrations for formula-fed infants assumed to consume infant formula with the lowest iodine content (108 mcg/L) was within the range of urinary iodine concentrations range reported in the literature for infants fed both cow milk-based and soy-based infant formulas, but as mentioned previously, additional studies could be included regarding the iodine content of infant formulae. For infant formulas with the highest iodine content (384 mcg/L), model-predicted urinary iodine concentrations were only within the range of those consuming cow milk-based formula, which is reasonable. Model-predicted urinary perchlorate concentrations were within the range of those reported in the literature for the perchlorate content of cow milk- and soy milk-based infant formulas.

- Figure 5 (Urinary iodine for breastfed infants): The model-predicted urinary iodine concentrations for breastfed infants are also within the range of those reported in the literature at postnatal days 45-90, although as noted previously, there are limitations to the calibration of breastmilk and urinary iodine concentrations used in the model. Average maternal perchlorate dietary intake was estimated and assumed to be 100 ng/kg/day for these calibrations. Also noted is that the model for urinary iodine in breastfed infants is not within the range of literature data for postnatal days 7-44, a similarly critical period of rapid infant neurodevelopment.
- Figure 6 (Urinary perchlorate for breastfed infants): These calibrations appear to be reasonable and within the range of literature-reported values among both formula-fed and breastfed infants from postnatal days 0-90, although as noted previously, there are limitations to the calibration of breastmilk and urinary perchlorate concentrations used in the model. Maternal dietary iodine intake between 75-250 mcg/day had no effect on predicting urinary perchlorate concentrations in their breastfed infants.
- Figure 7 (Breastmilk iodine and perchlorate): The potential issues of calibration against the published literature data is summarized above in Question 1B regarding the significant variability of breastmilk iodine content in relation to dietary iodine intake.
- Figure 8 (Maternal serum TT4 and FT4): The model-predicted values are comparable to existing literature from NHANES cohorts, but significant limitations include the lack of assessment of thyroid autoantibody positivity and other variables (see my responses to Question 1B), as well as the extremely small size of this cohort upon which the model is based. Model simulations were performed for maternal dietary iodine intakes from 75-250 mcg/day and an assumed maternal perchlorate exposure of 100 ng/kg/day.
- Figure 9 (Serum TT4 and FT4 for breastfed infants; no literature available for formula-fed infants): The model-predicted serum thyroid hormone values are comparable to existing literature, although as noted previously, there are limitations to the calibration of serum thyroid hormone concentrations used in the model. Although a maternal dietary intake of 75 mcg/day predicts serum TT4 and FT4 concentrations much lower than those for higher dietary iodine intakes (150-250 mcg/day), the serum thyroid hormone concentrations of their breastfed infants remain within the range during postnatal days 7-90.

Michael H. Lumpkin, Ph.D., DABT

The model appears to adequately predict iodide, perchlorate, and thyroid hormone levels in various matrices in all of the evaluated life stages. In the lactating mother, the model captured well the observed postpartum levels of iodide and perchlorate in milk (reflecting the performance of the NIS M-M parameters, as adjusted for this model) as well as serum fT4 levels that are in the range (9-12 pM) for which dose-response analyses were recommended. The same appears to hold true for urinary iodide and perchlorate and serum fT4 simulations in breast-fed infants. An expansion of the model to include the 1st trimester of gestation would allow the analysis of large cohort data sets, with exposure range estimates, to further indicate the level of model predicative precision.

Elizabeth N. Pearce, M.D., M.Sc.

Please see Table 4 (reference ranges for thyroid function in early pregnancy) and Table 7 (hypothyroxinemia & adverse obstetrical and neonatal outcomes) from the recent American Thyroid Association thyroid in pregnancy guideline (Alexander, Pearce et al. Thyroid. 2017 Mar;27(3):315-389. doi: 10.1089/thy.2016.0457).

Studies with trimester-specific thyroid function reference ranges (all studies excluded TPO antibody positive women):

Bocos-Terraz JP, Izquierdo-Alvarez S, Bancalero-Flores JL, Alvarez-Lahuerta R, Aznar-Sauca A, Real-López E, Ibáñez-Marco R, Bocanegra-García V, Rivera-Sánchez G. Thyroid hormones according to gestational age in pregnant Spanish women. BMC Res Notes. 2009;2:237. *[cohort is mildly iodine deficient]*

Gilbert RM, Hadlow NC, Walsh JP, Fletcher SJ, Brown SJ, Stuckey BG, Lim EM. Assessment of thyroid function during pregnancy: first-trimester (weeks 9-13) reference intervals derived from Western Australian women. Med J Aust. 2008;189(5):250-3. *[borderline iodine deficient cohort]*

Lambert-Messerlian G, McClain M, Haddow JE, Palomaki GE, Canick JA, Cleary-Goldman J, Malone FD, Porter TF, Nyberg DA, Bernstein P, D'Alton ME; FaSTER Research Consortium. First- and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First- and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study. Am J Obstet Gynecol. 2008;199(1):62.e1-6 *[mildly iodine deficient cohort]*

La'ulu SL, Roberts WL. Ethnic differences in first-trimester thyroid reference intervals. Clin Chem. 2011;57(6):913-5. *[mildly iodine deficient cohort]*

Zhang X, Yao B, Li C, Mao J, Wang W, Xie X, Teng X, Han C, Zhou W, Li C, Xu B, Bi L, Meng T, Du J, Zhang S, Gao Z, Yang L, Fan C, Teng W, Shan Z. Reference Intervals of Thyroid Function During Pregnancy: Self-Sequential Longitudinal Study Versus Cross-Sectional Study. Thyroid. 2016;26(12):1786-1793. *[iodine sufficient cohort]*

Pearce EN, Oken E, Gillman MW, Lee SL, Magnani B, Platek D, Braverman LE. Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking, and multivitamin use. Endocr Pract. 2008;14(1):33-9. *[likely iodine sufficient or borderline cohort, but not assessed]*

Männistö T, Surcel HM, Ruokonen A, Vääräsmäki M, Pouta A, Bloigu A, Järvelin MR, Hartikainen AL, Suvanto E. Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population. Thyroid. 2011;21(3):291-8. *[iodine sufficient cohort]*

Bestwick JP, John R, Maina A, Guaraldo V, Joomun M, Wald NJ, Lazarus JH. Thyroid stimulating hormone and free thyroxine in pregnancy: expressing concentrations as

multiples of the median (MoMs). Clin Chim Acta. 201;430:33-7. *[cohort is mildly-moderately iodine deficient]*

Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, Hofman A, Hooijkaas H, Steegers EA, Tiemeier H, Bongers-Schokking JJ, Visser TJ. Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R study. J Clin Endocrinol Metab. 2012;97(2):646-52. *[iodine sufficient cohort]*

Quinn FA, Gridasov GN, Vdovenko SA, Krasnova NA, Vodopianova NV, Epiphanova MA, Schulten M. Prevalence of abnormal thyroid stimulating hormone and thyroid peroxidase antibody-positive results in a population of pregnant women in the Samara region of the Russian Federation. Clin Chem Lab Med. 2005;43(11):1223-6. *[moderately iodine deficient cohort]*

Springer D, Zima T, Limanova Z. Reference intervals in evaluation of maternal thyroid function during the first trimester of pregnancy. Eur J Endocrinol. 2009;160(5):791-7. *[mildly iodine deficient cohort]*

Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab. 2007;92(1):203-7. *[mildly to moderately iodine deficient cohort]*

Studies investigating links between maternal hypothyroxinemia in pregnancy and adverse child developmental outcomes:

Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, Palomaki GE, Neveux LM, Haddow JE. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab. 2012;97(1):E22-8.

Finken MJ, van Eijsden M, Loomans EM, Vrijkotte TG, Rotteveel J. Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring. J Clin Endocrinol Metab. 2013;98(4):1417-26.

Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R, Lertxundi N, Espada M, Tardón A, Riaño Galán I, Sunyer J. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology. 2013;24(1):150-7.

Ghassabian A, El Marroun H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Tiemeier H, White T. Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. J Clin Endocrinol Metab. 2014;99(7):2383-90.

Gyllenberg D, Sourander A, Surcel HM, Hinkka-Yli-Salomäki S, McKeague IW, Brown AS. Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort. Biol Psychiatry. 2016;79(12):962-70.

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Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. JAMA Pediatr. 2015;169(9):838-45.

Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol. 2016;4(1):35-43.

Additional data for U.S. infant formula iodine and perchlorate concentrations can be found in:

Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentin-Blasini L, Braverman LE. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab. 2007;92(5):1673-7.

The following study includes data on radioactive iodine uptakes following ingestion of perchlorate doses ranging from 0.5 mg/d to 3 mg/d in healthy volunteers and could be another source, in addition to Greer et al, to use for model validation:

Braverman LE, Pearce EN, He X, Pino S, Seeley M, Beck B, Magnani B, Blount BC, Firek A. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. J Clin Endocrinol Metab. 2006;91(7):2721-4.

A new balance study in formula-fed 2-month-old infants is highly relevant:

Dold S, Zimmermann MB, Baumgartner J, Davaz T, Galetti V, Braegger C, Andersson M. A dose-response crossover iodine balance study to determine iodine requirements in early infancy. Am J ClinNutr. 2016 Sep;104(3):620-8.

The following studies have examined maternal thyroid function in relation to iodine and perchlorate exposure in pregnancy (at various stages of gestation) and might be used to help with model calibration, especially if, as I would recommend, the model is expanded to examine the first two trimesters of pregnancy:

Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. Thyroid Hormones and Moderate Exposure to Perchlorate during Pregnancy in Women in Southern California. Environ Health Perspect. 2016;124(6):861-7.

Charatcharoenwitthaya N, Ongphiphadhanakul B, Pearce EN, Somprasit C, Chanthasenanont A, He X, Chailurkit L, Braverman LE. The association between perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant Thai women. J Clin Endocrinol Metab. 2014;99(7):2365-71.

Pearce EN, Alexiou M, Koukkou E, Braverman LE, He X, Ilias I, Alevizaki M, Markou KB. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women from Greece. Clin Endocrinol (Oxf). 2012;77(3):471-4.

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Pearce EN, Spencer CA, Mestman JH, Lee RH, Bergoglio LM, Mereshian P, He X, Leung AM, Braverman LE. Effect of environmental perchlorate on thyroid function in pregnant women from Córdoba, Argentina, and Los Angeles, California. Endocr Pract. 2011;17(3):412-7.

Pearce EN, Lazarus JH, Smyth PP, He X, Dall'amico D, Parkes AB, Burns R, Smith DF, Maina A, Bestwick JP, Jooman M, Leung AM, Braverman LE. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. J Clin Endocrinol Metab. 2010;95(7):3207-15

Horton MK, Blount BC, Valentin-Blasini L, Wapner R, Whyatt R, Gennings C, Factor-Litvak P. Co-occurring exposure to perchlorate, nitrate and thiocyanate alters thyroid function in healthy pregnant women. Environ Res. 2015;143(Pt A):1-9.

Mortensen ME, Birch R, Wong LY, Valentin-Blasini L, Boyle EB, Caldwell KL, Merrill LS, Moye J Jr, Blount BC. Thyroid antagonists and thyroid indicators in U.S. pregnant women in the Vanguard Study of the National Children's Study. Environ Res. 2016;149:179-88.

Studies regarding age-normative thyroid function in early infancy:

Elmlinger MW, Kühnel W, Lambrecht HG, Ranke MB. Reference intervals from birth to adulthood for serum thyroxine (T4), triiodothyronine (T3), free T3, free T4, thyroxine binding globulin (TBG) and thyrotropin (TSH). Clin Chem Lab Med. 2001;39(10):973-9.

Chaler EA, Fiorenzano R, Chilelli C, Llinares V, Areny G, Herzovich V, Maceiras M, Lazzati JM, Mendioroz M, Rivarola MA, Belgorosky A. Age-specific thyroid hormone and thyrotropin reference intervals for a pediatric and adolescent population. Clin Chem Lab Med. 2012;50(5):885-90.

Studies/data characterizing the TH regulation in pregnancy and in non-pregnant women of childbearing age include:

Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? Clin Chem. 2015 May;61(5):704-13.

Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, Li C, Xu B, Bi L, Meng T, Du J, Zhang S, Gao Z, Zhang X, Yang L, Fan C, Teng W. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? J Clin Endocrinol Metab. 2014 Jan;99(1):73-9.

Stephen M. Roberts, Ph.D.

See response to this comment by Dr. Pearce.

Joanne F. Rovet, Ph.D.

YES for iodine and perchlorate and breast milk. NO for thyroid hormone/iodine and perchlorate. However, as I found the Results section messy and not clear, I cannot adequately judge how well the model agrees with the extant literature for iodine and perchlorate concentrations in urine and breast milk. The only study to examine these is Leung et al. (2012), which found no effect of breast milk perchlorate on infant thyroid hormone levels.

Question 3B. Are the influential parameters identified in the local sensitivity analysis for total thyroxine (T4) and free thyroxine (fT4) plasma concentrations consistent with known biology? Are there critical data gaps for the influential parameters, which would impact the thyroid hormone predictions? If gaps are identified, please provide approaches that would improve thyroid hormone predictions.

Hugh A. Barton, Ph.D.

This reviewer cannot comment on whether the "influential parameters" are "consistent with known biology". There are descriptions in Tables 4 and 5 of the basis for the values for these influential parameters and there does appear to be some data available for each, though it is difficult to evaluate how well it determines each parameter.

I would also advocate that sensitivity analyses be carried out for the model outputs and exposure scenarios that get compared to data, e.g., plasma, urinary, or breast milk concentrations or iodine or thyroid hormones. This helps clarify which parameters the data are sensitive to and thus, which parameters are reasonably calibrated or evaluated with the data. The sensitivity analyses presented on plasma hormone levels are useful for indicating what parameters drive the model outputs anticipated to be utilized in further development of the MCLG.

Claude Emond, Ph.D.

The sensitivity analysis (SA) discussed in the report tested the influence of the new parameters, which were also described for the iodine description, and discussed whether there was a presence of exogenous perchlorate and iodine. The analysis and synthesis performed in this report are not descriptive enough. The report should include more detailed discussions so the readers will understand the impact of each parameter. Currently, based on the SA each parameter seems to have a similar impact in the prediction of the model. It is difficult to extract the sensitive parameters that drive the simulation.

Dale Hattis, Ph.D.

The influential model parameters seem to have been identified, but I am not satisfied with the generally subjective procedures used to judge whether the existing set of parameter values leads to model predictions that reasonably correspond to model predictions, or whether better model predictions are possible using improved sets of parameter values.

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Angela M. Leung, M.D., M.Sc.

Comments regarding sensitivity analyses for serum TT4 and FT4 concentrations:
The analyses reported on pages 83-91were reviewed, from which the main findings are summarized as below.

- Results for infant serum TT4 and FT4 concentrations are identical, and thus only infant serum T4 concentrations are reported.
- Influential parameters were time-dependent, iodine-dependent, and perchlorate-dependent.
- Given the relatively lower iodine content in breastmilk, as compared to infant formula, the effect of perchlorate exposure was more significant in the analyses which examined perchlorate exposure from breastmilk.

These findings are generally consistent with the available knowledge regarding factors which may influence serum thyroid hormone concentrations. However, as described in my response to Question 4A, it would be prudent to also examine the influence of serum thyroid autoantibody positivity on serum thyroid hormone concentrations in these sensitivity analyses.

Michael H. Lumpkin, Ph.D., DABT

Although the report states that the most influential parameters are time-, iodide-, and perchlorate-sensitive (p84), Figures 19-20 and Tables 11-12 do not seem to support this, except for the day 7 influence for both formula and breast-fed infants. The influence of daily T4 production (VPRODT4CX) and 1st order T4 clearance (CLMETT4CX) parameter values have far more impact than parameters that influence perchlorate-related changes to iodide transport into the thyroid and breast milk, which is surprising. If that is the case for this model, some discussion in the report of why that is the case may be helpful.

Elizabeth N. Pearce, M.D., M.Sc.

Sensitivity analyses used to determine influential parameters for total and free T4 concentrations in formula- and breast-fed infants included a range of iodine exposures (from 75-200 mcg daily for mothers and breastfed infants, and from 108-384 mcg/L formula for the formula-fed infants) and of perchlorate exposures (from 0-20 mcg/kg/day) for both mothers and infants. The range of perchlorate exposures chosen for testing seems reasonable. However, it should be noted that the range for infant formula iodine concentrations some from one of my studies (Pearce et al. 2004), and I am not sure that values are representative of U.S. brands. We subsequently published a paper listing the iodine content of a wider variety of infant formulas which, while still not necessarily nationally representative, may be a bit better (Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentin-Blasini L, Braverman LE. J Clin Endocrinol Metab. 2007;92(5):1673-7. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab. 2007;92(5):1673-7). In addition, there is a very wide range of allowable infant formula iodine content for full-term infants in the U.S: 5 to 75 μg/100 kcal (33.5–507.2 μg/L) (U.S. Food and Drug Administration 2006Code of Federal Regulations 21CFR107 Infant formula.
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=107&showF

R=1). Therefore, the sensitivity analyses did not account for potentially much lower iodine exposures in formula-fed infants which presumably could occur in the U.S.

It is logical that rates of T4 to FT4 conversion, rates of T4 production in the infant thyroid, and rates of thyroid hormone metabolism would be the highly influential parameters for the FT4 models. In the breastfed infants, the influence of intrathyroidal iodine stores (CTGIPOOL_N) is a stronger influence at day 7 of life than at day 90; this makes sense in light of the fact that intrathyroidal iodine turnover is highest in the immediate neonatal period.

Stephen M. Roberts, Ph.D.

During the face-to-face meeting, there seemed to be near consensus that the sensitivity analysis was not well conducted or presented. This is an extremely important aspect of the model evaluation and in assessing the uncertainty of model predictions. Greater emphasis should be placed on identifying the influential parameters and presenting clearly the influence of choices made regarding these parameters on model predictions. Once this has been done, it will be easier to evaluate the extent to which the influence of these parameters is consistent with known biology.

Joanne F. Rovet, Ph.D.

I am not able to answer this given the way the information is presented. I would have liked a closer match between the categories in Table 7 and the models in Figures 2 and 3.

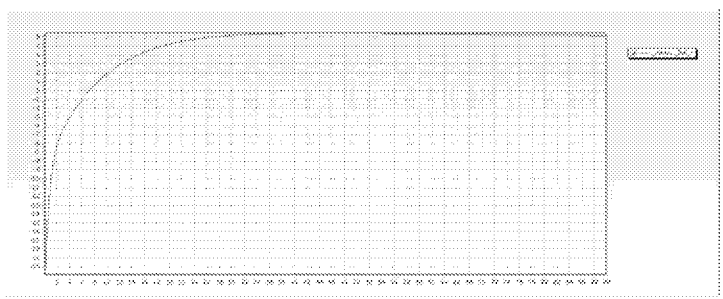
Question 3C. Does the proposed model provide the appropriate level of precision and substantiated support for this approach? Please identify any additional limitations of the model's applicability?

Hugh A. Barton, Ph.D.

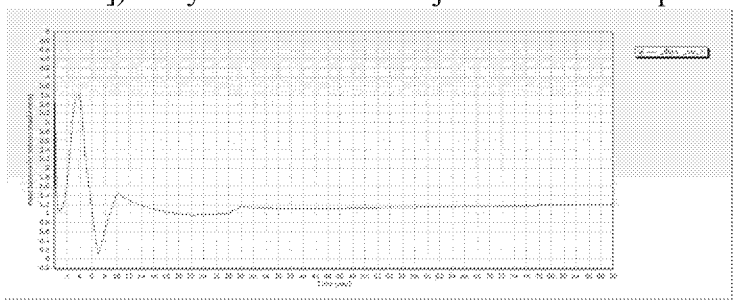
Presumably, "this approach" refers to using the model to assess potential perchlorate dose-response. Various limitations of the effort are noted in the report and the comments here.

Claude Emond, Ph.D.

The mass balance for the maternal iodine (Bal_i [see line 1561 of the code in acslX]) should be checked (see the figure below). For iodine, the mass balance is probably a minor error, but it should be corrected.



As can be seen in the figure below, there is also an issue regarding the mass balance for the infant (Bal_Ni [see code line 1577]). Maybe a correction or justification is required.



The mass balance for the weight and the volume are both fine for the mother and the infant. I am unsure why the authors doubled the volume and the blood flow for perchlorate and iodine? If the model is updated rather to add another submodel the integration of all pieces in a one framework would be required. In addition, it is possible also to incorporate in the same PBPK model structure women having not pregnant, pregnant and nursing conditions for the lifetime exposure using different conditions exposure scenario.

Dale Hattis, Ph.D.

This cannot be adequately evaluated with the comparison plots provided.

Angela M. Leung, M.D., M.Sc.

Comments regarding model precision:

There are several limitations, as mentioned elsewhere in this report, which may limit the precision and substantiated support of the model.

In addition, there was a recent publication estimating the perchlorate burden from dietary intake as part of the FDA's Total Diet Study (Abt E et al, PMID 28000685), which can be cited to support the range of perchlorate exposure levels assessed in the model.

Michael H. Lumpkin, Ph.D., DABT

The performance of the model in replicating concurrent milk and urine iodine and perchlorate data in the lactating mother, and perchlorate and serum fT4 in the breast-fed infant in the space of perchlorate exposure and thyroid hormone levels for which that model is intended be utilized indicates sufficient precision of the model for use in dose-response assessment.

Elizabeth N. Pearce, M.D., M.Sc.

I do not have expertise in model development, so I am unable to comment on this question.

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Stephen M. Roberts, Ph.D.

The appropriate level of precision depends upon the use of the model outputs and tolerance for inaccuracy and uncertainty. Consequently, the answer to this question requires risk management input. However, to answer the question whether the level of precision is appropriate, some sense of the precision — and accuracy — of the model are needed. The accuracy of the model in particular is difficult to judge because comparisons of model outputs with literature values from humans in the report are few and variability in human populations for parameters used to check model outputs (e.g., urinary perchlorate, urinary iodide) are large. On the positive side, model inputs are not out of line with human data for the comparisons shown in the report. On the other hand, variability is large enough in the human comparison data that the model predictions could in some cases be substantially different and still be as concordant.

Joanne F. Rovet, Ph.D.

I was not able to fully comprehend the meaning of the data in Figures 18-20 or Tables 11-12 as they contained what seemed to me to be just raw data or statistical output with little attempt to synthesize these data. No statistics are presented and the Figures lack legends that might allow one to zero in on key findings. Global comparison of the three figures suggests to me a greater impact of perchlorate at Day 7 in the formula-fed than breast-fed infant at the low iodine level; in the mother, this perchlorate effect took place later. I am not sure how my "eye-balling" conforms with the graphs provided.

Question 4. Hypothyroxinemic reference levels and model predictions: The SAB (2013) recommended that the EPA focus the application of BBDR modeling on the condition of hypothyroxinemia, in which circulating levels of free thyroxine (fT4) are reduced below the normal ("reference") range, but with normal levels of thyroid stimulating hormone (TSH). While the mode of action (MOA) for perchlorate is well described, a defined set of quantitative definitions for reference ranges for hypothyroxinemia during pregnancy or lactation and in infants is not available. For interpretation of the BBDR model, EPA developed a normalization procedure to derive hypothyroxinemia reference intervals and to control for the expected differences between literature results and model predictions.

Question 4A. Please comment on the hypothyroxinemia reference ranges derived for pregnant mothers, fetuses, lactating mothers, breast-fed infants and bottle-fed infants. Is the assumed range between the 2.5th and 10th percentile of the fT4 distribution reasonable? Is it supported by the available data? Has the derivation of the reference ranges, including the normalization process, been appropriately described and supported in the model and the report?

Hugh A. Barton, Ph.D.

This reviewer cannot comment on the range of iodine intake levels beyond indicating that the approach of using a range of values appears a valuable one. Based upon the discussions at the peer review meeting, I agree that the use of defined reference ranges to discriminate when this model for isolated hypothyroxinemia is applicable or not (i.e., hypothyroidism that would

require description of TSH-mediated feedback processes) is reasonable. The use of these reference ranges for purposes beyond that, e.g., defining changes to be considered adverse, does not appear appropriate because it dichotomizes a continuous response and, perhaps more importantly, focuses on a precursor event without defining its relationship to the critical neurodevelopmental outcomes.

Claude Emond, Ph.D.

As mentioned in page 17 of the report, there has been no consensus in the literature regarding the limit between euthyroid and hypothyroxinemia condition; therefore, determining this by using the range of fT4 is reasonable inside the range describe by the authors. As a first step this is OK, however a better characterization of the impact of this range between the 2.5th and 10th percentile of the fT4 particularly in a subpopulation not exposed to perchlorate or with deficiency in iodine.

Dale Hattis, Ph.D.

I think these choices of reference ranges are completely arbitrary and not founded without well-grounded justification in biology. As indicated earlier, I think it would be best to use the thyroid hormone predictions from exposures to perchlorate in early pregnancy to estimate expected population-wide changes in expected IQ's for the offspring of the pregnancies. This endpoint would provide much more meaningful information for juxtaposing expected costs and benefits of regulatory actions to alter perchlorate exposures.

Angela M. Leung, M.D., M.Sc.

Comments regarding hypothyroxinemia reference ranges:
Page 17 (lines 12-21) outlines the model's definition of hypothyroxinemia, which are described as serum FT4 concentrations for pregnant mothers, lactating mothers, breastfed infants, and formula-fed infants in the 2.5-10th percentile of the general population. Euthyroxinemia in the model is defined as serum FT4 concentrations in the 10-90th percentile. The selected reference range for hypothyroxinemia also assumes that overt hypothyroidism (i.e., an elevated serum TSH concentration with low serum FT4 concentration) occurs when serum FT4 concentrations are in the <2.5th percentile range. These parameters were chosen due to a lack of a universal definition for hypothyroxinemia in these population subgroups from the available literature. The following are some considerations, particularly regarding the limitations surrounding the definition of hypothyroxinemia during pregnancy:

- Thyroid hormone levels are dependent on the prevalence of thyroid autoantibodies in the population examined, which was not accounted for in the current model. Positive thyroid autoantibodies carry up to a 5-fold risk of hypothyroidism in geographic regions of iodine sufficiency (Moleti M et al; PMID 19179457).
- The accuracy of serum FT4 immunoassays in pregnancy has been questioned (Lee RH et al; PMID 19114271), due to their dependence on thyroid binding proteins.
- A recent review provides a comprehensive summary of this topic during pregnancy and should be included as a reference (Negro R et al; PMID 21247845).

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Michael H. Lumpkin, Ph.D., DABT

The review of Moleti et al. (2011) cites 10 published studies of pregnant women in which threshold hypothyroxinemia was defined as the 2.5th or 10th percentile of fT4 in the respective cohort. As pointed out in the report, the fT4 levels represented in these percentiles are variable, likely being owed to cohort-specific fT4/TSH characteristics or differences in laboratory analytical capabilities brought to bear on each cohort's analysis of thyroid hormones. The normalization of study-specific thyroid hormone means for euthyroid and hypothyroid women is justified in order to use a single BBDR model to be used for dose-response analyses based on disparate data sets. The normalization procedure described in the report appropriately adjusts the "normal" and hypothyroxinemic ranges reported in the literature.

Elizabeth N. Pearce, M.D., M.Sc.

The existing literature regarding effects of maternal hypothyroxinemia in pregnancy variably uses thresholds of the 2.5th, 5th, or 10th percentile to define the condition (again, see Table 7 in the recent ATA thyroid in pregnancy clinical guideline; Alexander, Pearce et al. Thyroid [Epub]).. Therefore, I think this range is reasonable in pregnancy. A similar normalization approach for maternal thyroid function across different assay platforms has recently been described: Bestwick JP, John R, Maina A, Guaraldo V, Joomun M, Wald NJ, Lazarus JH. Thyroid stimulating hormone and free thyroxine in pregnancy: expressing concentrations as multiples of the median (MoMs). Clin Chim Acta. 2014;430:33-7.

There is currently no accepted clinical definition of isolated hypothyroxinemia outside of the pregnancy setting. In the absence of an accepted definition at these life stages, using the 2.5th to 10th percentile of the fT4 distribution is reasonable. Note, however, that this level may change over the course of the first 90 days of life. Publications describing age-normative thyroid function values for infants are listed in 3A.

Stephen M. Roberts, Ph.D.

The SAB Perchlorate Advisory Panel noted the following in their report: "Perhaps most critical are the findings from studies examining the effects of isolated maternal hypothyroxinemia, defined as a free thyroxine (fT4) value in the lower end of the normal range with normal levels of TSH. This research has involved a variety of cutoffs to signify maternal hypothyroxinemia ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile (Moleti et al. 2011), with the former percentiles being used to investigate neurodevelopmental outcomes and the latter the incidence and effects on pregnancy (e.g., Casey et al. 2005). Children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al. 1991; Pop et al. 1999; Pop et al. 2003; Kooistra et al. 2006). Notably these effects are correlated with both degree (Pop et al. 1999; Henrichs et al. 2010) and duration (Pop et al. 2003) of maternal hypothyroxinemia. The Henrichs (2010) study, which stratified children into severe (<5th percentile) and mild (5-10th percentile) maternal hypothyroxinemia subgroups, showed that while effects were stronger and broader in the severe subgroup, the mild subgroup still showed

delayed language development, thus suggesting that any factor that lowers maternal fT4, even slightly, can affect the offspring." (SAB 2013; pg. 10).

Using the 10th percentile of the fT4 distribution as the upper end of the range is reasonable and consistent with the discussion presented by the SAB panel for pregnant women relative to risk to the fetus. There is some question regarding using the 2.5th percentile as the lower end. The reason for setting this lower limit is not based upon risk of neurodevelopmental effects (which continue to exist at even lower fT4 values), but instead on fT4 values below which increased TSH is expected, and the model cannot currently predict fT4 under those conditions. This assumption that the 2.5th percentile for fT4 is an appropriate cut-off with respect to compensatory TSH secretion is based upon data from Silva and Silva (1981), but the reliability of those data was questioned during the face-to-face panel meeting due in part to limitations in technology available for measurements at that time. At present, scientific support for the lower reference range cut-off of the 2.5th percentile is not strong.

The charge question also asks about other life stages. As discussed in the response to Charge Question 1C, modeling of fetal thyroid hormone changes is unnecessary and problematic. The rationale for modeling fT4 in lactating women should be better explained in the report, as it is not a sensitive life stage and transfer of fT4 from mother to infant in breast milk is not significant.

Understanding thyroid hormone changes in breast-fed and bottle-fed infants is important, but a clearer case needs to be made why the range between the 2.5th and 10th percentile of the fT4 distribution is appropriate. There is ample evidence for susceptibility to neurodevelopmental deficits from thyroid deficits in infancy, but I am not aware of data that associates risk directly with hypothyroxinemia in infancy as defined using these fT4 percentiles. If there are studies to support this choice, they should be cited; if not, this should be characterized instead as perhaps a conservative assumption.

Joanne F. Rovet, Ph.D.

I disagree with this reference range. Most studies (of mothers) use a value below the 5th percentile and when studies do examine mother-child pairs with maternal values up to the 10th percentiles, these are done in a correlational design with results showing no or very mild effects for offspring of mothers with mild (i.e., 5th to 10th percentile) hypothyroxinemia. I would also like to see effects of values below 2.5th percentile and the impact on subclinical or compensated hypothyroidism. It is not a given that TSH is elevated when fT4 is below the 2.5th percentile nor not elevated when above this value. There are to my knowledge no reference levels for hypothyroxinemia in infants.

Note that I was one of the writers of the cited section of the SAB-PAP report. Rereading the section and recalling the discussion, it wasn't that these findings (i.e., hypothyroxinemia) were more critical than those on subclinical hypothyroidism; rather, these findings were relevant in that even a low fT4 with a normal TSH, particularly when the fT4 was below the 5th percentile, had consequences for later offspring outcome. In other words, this interpretation is taken out of context. Furthermore, the decision to exclude TSH seems to be based totally on an old (1981)

paper by Silva and Silva, I believe from Chile, and this needs to be supported by more recent evidence.

Question 4B. Model predictions for zero intake of perchlorate indicate the range of iodine ingestion for which these life-stages are expected to be euthyroid vs. hypothyroxinemic. Are these predictions reasonable and have they been appropriately described and supported in the model and the report?

Hugh A. Barton, Ph.D.

This reviewer cannot comment on the range of iodine intake beyond noting that the descriptions in the report appeared clear.

Claude Emond, Ph.D.

The predictions and descriptions are appropriate to support the model.

Dale Hattis, Ph.D.

As far as I can tell at this stage, there is every expectation that some people in iodine deficient areas and elsewhere will be hypothyroxinemic at zero perchlorate exposure. This should be checked against actual NHANES data and juxtaposed with information on local water perchlorate levels in the areas where the NHANES subject resided.

Angela M. Leung, M.D., M.Sc.

Comments regarding the effects of zero perchlorate exposure and iodine ingestion on serum thyroid function:

Perchlorate exposure will invariably co-occur with other thyroid toxicants, many of which are similarly ubiquitous and also have inhibitory effects on iodine at NIS. The best well-described known examples are thiocyanate and nitrate, and their effects should be included in the model. As such, zero perchlorate exposure cannot necessarily be assumed to result in serum thyroid function changes resulting from iodine intake alone, but rather as a combined result from other coexposures and iodine intake. However, of these three known NIS inhibitors, perchlorate has been demonstrated to have the strongest effect in competitively inhibiting iodine uptake at NIS (Tonacchera et al; PMID 15650353).

Michael H. Lumpkin, Ph.D., DABT

The ranges of euthyroid (<100 µg/day) and hypothyroxinemic (75 µg/day or less) iodide intake levels for the BBDR model are appropriately described in the report. The report repeatedly warns of the uncertainty in model predictions of fT4 levels at iodide levels in the hypothyroxinemic range, as TSH-mediated regulation of iodide transport and T4 production are expected to be activated.

Elizabeth N. Pearce, M.D., M.Sc.

Figures depicting the dose-response curves for free T4 across perchlorate exposures are challenging to interpret as currently presented. However, it is noted on page 18 that at 75 mcg/day iodine ingestion pregnant and lactating women are assumed to be hypothyroid, and that at <100 mcg/day iodine intake the fT4 approaches the lower end of the maternal reference ranges even in the absence of perchlorate exposure. In reality, the literature demonstrates that at those iodine intakes there is a wide range of maternal thyroid function values, likely reflecting substantial intraindividual variations in adaptive capacity, and although median TSH might be higher in populations of pregnant or lactating women with iodine ingestion 75 mcg/L than in those with adequate iodine intakes, the vast majority of women likely would not be hypothyroid. It is for that reason, that serum TSH, free T4, and T3 are considered highly insensitive as biomarkers for population or individual iodine status in adults, including pregnant and lactating women (Pearce EN, Caldwell KL. Urinary iodine, thyroid function, and thyroglobulin as biomarkers of iodine status. Am J Clin Nutr. 2016;104 Suppl 3:898S-901S). This is, in part, which I think it is important to include the full HPT axis in the models. (Note that, unlike for other life stages, TSH values in neonates may be used to characterize population iodine status. See Delange F. Screening for Congenital Hypothyroidism Used as an Indicator of the Degree of Iodine Deficiency and of its Control. Thyroid. 2009, 8(12): 1185-1192.)

For breastfed infants, if 75 mcg/day maternal iodine ingestion was assumed for pregnancy and maternal intake in lactation was <100 mcg/day, the model suggests that FT4 is low even in the absence of perchlorate exposure. This assumption may be overly conservative, but is reasonably well supported by data in the report.

Stephen M. Roberts, Ph.D.

Providing model predictions of fT4 levels with zero intake of perchlorate should provide an opportunity to check the accuracy of predictions, but unfortunately there are few studies relating iodine intake and fT4 levels in the life stages of interest. For example, the modeling predicts that a pregnant or lactating woman with 75 µg/d iodine intake and no perchlorate exposure will be hypothyroid. I found no study that indicates whether or not this prediction is plausible, and the report itself provides no discussion of the reasonableness of the estimates. So, while the predictions are described, they are not supported [as valid] in the report.

Joanne F. Rovet, Ph.D.

I don't understand the question. Hypothyroxinemia in the 5-10% range is not to me a problem of concern for the developing infant. There are no data examining infant fT4 levels in this range and later outcome. Note: most concern for later outcome has generally reflected the maternal state throughout pregnancy and not the neonatal state in children who do not have congenital hypothyroidism. However, a recent study by C Trumpff et al. (2016, Frontiers in Endocrinology) that examined the relationship between elevated TSH levels at birth and preschool-age behavior problems in an area of mild iodine deficiency reported no association. Further, Oken et al. (2009, JCEM) studying the relationships between neonatal fT4 levels (all levels) and subsequent abilities reported an *inverse* relationship with visual recall at 6 months and no relationship with language or visuomotor development at age 3 years.

Question 4C. Based on the perchlorate level at which each life stage is predicted to become hypothyroxinemic (for a given iodine ingestion rate), it appears that the lactating mother is more sensitive than the breast-fed infant for PND 30-90. In part, this occurs because breast feeding reduces the iodide available for the maternal thyroid. Are these predictions reasonable and have these predictions been appropriately described and supported in the model and the report?

Hugh A. Barton, Ph.D.

This reviewer cannot comment on the reasonableness of these predictions, though they appear well described in the report. Perhaps part of evaluating the reasonableness is to ask what the implications of hypothyroxinemia are for the lactating mother versus the breast-fed infant. For the infant, the concern would be impacts on neurodevelopment. Is the issue for the lactating mother, a direct impact on her heath or a concern for inadequate levels of iodine and/or thyroid hormones in breast milk for the infant? If the former, then the lactating mother's sensitivity would be an endpoint to consider, but if it is the latter, then despite the apparently greater sensitivity of the mother, the direct predictions for the infant would seem more relevant. Discussions at the peer review meeting strongly indicated that the concern is for the neurodevelopment of the infant so a focus on the predictions for the mother was not appropriate.

Claude Emond, Ph.D.

The prediction of the model is reasonable based on the prediction presented in the report (see Figures 4, 5, 6, and 7). This is true for the mother and infant prediction during lactation or none. However, there is a lack of data, so we do not have enough information to qualify the risk for the fetus. The authors of this report expressed very well the limitation and applicability of this model (pages 16 to 22). Also, it seems that the influence of perchlorate, iodine or both exposure has a higher impact from exposure to perchlorate during breast feeding.

Dale Hattis, Ph.D.

This seems reasonable. However, it is best evaluated by drawing on the empirical information generated with the information assembled via my response to question 4B, separated by pregnant vs lactating women subgroups.

Angela M. Leung, M.D., M.Sc.

Comments regarding hypothyroxinemia in the lactating mother at PND 30-90:

- Breastfeeding does require a greater available iodine supply to the mother, and thus the U.S. Institute of Medicine recommends a slightly higher Recommended Dietary Allowance (RDA) of iodine during lactation then pregnancy (although the WHO/UNICEF/IGN just recommends an overall higher daily intake during both pregnancy and lactation, compared to the non-pregnant, non-lactating adult).

Assuming that this is the primary mechanism for the increased vulnerability of the lactating mother, it should be anticipated that the prediction would also hold true for the entire postnatal duration studied in the model, which is not suggested. Thus, model calibration parameters may be still be inexact in the model's present form.

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Michael H. Lumpkin, Ph.D., DABT

The conceptual reasoning given in the report that the lactating mother is more sensitive than the breast-fed infant because of additional iodide loss to the milk is biologically plausible. However, the report could include plots of simulations showing this relationship. For example, plasma iodide plotted against breast milk iodide levels across gestation, particularly at lower iodide intake rates, could illustrate this suggested phenomenon.

Elizabeth N. Pearce, M.D., M.Sc.

It is true that secretion of a significant amount of iodine into breast milk has the potential to make iodine unavailable for the lactating woman's own thyroid, a problem potentially exacerbated by the high dietary iodine requirements in lactation, as well as by perchlorate exposure. However, in thinking about populations sensitive to the effects of perchlorate, the concern with regard to lactating women does not pertain to their own hypothyroxinemia, but to the potential for inadequate supply of iodine in the breast milk, with potential adverse consequences for the thyroid hormone status and, ultimately, neurodevelopment of the breastfed infant. Therefore, as above, I think the concept of modeling maternal hypothyroxinemia in the lactating mother herself is somewhat flawed. It doesn't really make sense to describe the lactating mother as more sensitive to the effects of perchlorate than her breastfed infant at days 30-90 since transient maternal hypothyroxinemia over that time frame likely would not have long-term consequences for the mother, but could for the infant. Clinically, in the U.S. we do not see a higher-than-usual incidence of maternal hypothyroidism in lactation, (outside the setting of autoimmune postpartum thyroiditis), which does suggest to me that the model's predictions may not be correct. Calibrating the lactating women model against a more robust dataset may help to determine whether hypothyroxinemia is truly more likely to develop in lactating women than in their infants.

Stephen M. Roberts, Ph.D.

It is argued that the model result indicating that the lactating mother is more sensitive to hypothyroxinemia from perchlorate than her breast-fed infant is plausible because breastfeeding reduces iodine available for the maternal thyroid. This appears to be largely speculation. Appendix F includes a comparison of fT4 between lactating, pregnant, and "all other" women using data from NHANES. Although the fT4 levels in lactating women appear to be lower than "all other women", levels in pregnant women are even lower. I am not aware of any evidence from the literature that breastfeeding increases the risk of thyroid deficiency (even subclinical) and none is provided in the report. It is possible that this model prediction indicates a problem with the modeling of fT4 in the lactating mother, the breast-fed infant, or both.

Joanne F. Rovet, Ph.D.

I am not aware of any data to support this prediction. I am also not aware of any data comparing thyroid hormone levels of breast-feeding and formula-feeding mothers.

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Question 5. Robustness of model predictions and sensitivity at lower perchlorate dose levels:
The dose-response predictions from the BBDR model predict levels of fT4 for:
a) The pregnant mother and fetus at GW40 (Fig. 10);
b) The formula-fed infant with fixed (Fig. 11, 7 and 30 day infants) and variable (Fig. 12, 7 through 90 day infants) iodine levels in their formula; and
c) The breast-fed infant as a function of maternal perchlorate exposures and iodine ingestion (Fig. 13, 7 through 90 day infants).

For each of these subgroups, please characterize the extent of uncertainty along the dose-response curve. In particular, is the level of uncertainty acceptable at lower dose levels of perchlorate (e.g., at or below 4 µg/kg/d) and higher levels of iodine intake (e.g., 150 µg/d) for each of these subgroups (left upper corner of the dose-response curves)? Should EPA assume that the model becomes more uncertain with rising perchlorate dose levels and declining iodine ingestion, i.e., as model predictions for fT4 approach and move through the range of hypothyroxinemia. (It should be noted that calibration of the iodide and thyroid hormone sub-models used data for populations with higher iodine intake and background exposure to perchlorate.)

Hugh A. Barton, Ph.D.

For formula-fed and breast-fed infants, there was some data on urinary perchlorate in the 1 – 10 µg/L range that appears to somewhat inform lower perchlorate intake levels though it is difficult to assess how well it constrains the dose-response behavior of the model. It seems likely that the models becomes more uncertain with higher perchlorate exposures that result in greater inhibition and lower iodine levels, which at some point become hypothyroxinemia with elevated TSH that the model explicitly does not address.

Claude Emond, Ph.D.

These figures generated with the 2 PBPK models seem convincing that the models are sensitive enough inside of clinical range. However, they need now to be compared to the relevant exposure source of perchlorate in water.

Dale Hattis, Ph.D.

Again, I think these model predictions are best evaluated with empirical NHANES data separated into geographic categories by estimate levels of perchlorate in water. Because I am unconvinced by the calibration of the model as indicated earlier, I don't entirely trust the model predictions and have no basis to evaluate how much they are likely to be off.

Angela M. Leung, M.D., M.Sc.

Comments regarding model predictions and sensitivity at lower perchlorate levels in:
Figures 10-13 were reviewed with specific focus on the curves for lower perchlorate exposure and higher dietary iodine intake levels (left upper corner of the dose-response curves). In accordance with some of the public comments submitted thus far, it is reasonable to consider not

including those which calibration for the iodine and thyroid hormone submodels were not performed for, given the non-linear interdependence of iodine status with thyroid function –a relationship which is further complicated with the exposure to varying NIS inhibitors, including perchlorate. It is reasonable to assume that the models may be more uncertain for these areas which have not been calibrated for in the report.

Michael H. Lumpkin, Ph.D., DABT

With the exception of the formula-fed infant life stage, the assumption that the model predictions of fT4 become more uncertain as perchlorate exposure increases and iodide intake decreases appears to hold, particularly for the pregnant mother, based on the increasing proportion of the dose-response curves that move below the normalized 2.5th percentile level.

Elizabeth N. Pearce, M.D., M.Sc.

I think it is reasonable to assume for all of the models that there is a higher degree of uncertainty at both lower iodine and higher perchlorate exposure levels. There is likely less uncertainty in the formula-fed infant model, given that only adequate to above-adequate iodine intakes are assumed.

Stephen M. Roberts, Ph.D.

The model is predicated on the absence of a compensatory response throughout the predicted range of fT4 levels. This assumption becomes more tenuous with lower predicted fT4 levels; thus, it is correct to conclude that uncertainty in the results increases with rising perchlorate dose levels and declining ingestion.

Joanne F. Rovet, Ph.D.

a) First, what is GW40? – I assume it is parturition at 40-weeks gestation. Sorry, defined in figure caption, but should be listed in list of abbreviations. I found Figure 10 hard to interpret as the lines weren't clearly distinct from each other. I presume everything that is grey is bad and this includes most iodide exposures when perchlorate exceeds 11.7 pM. As I can't make sense of "uncertainties" from this graph (an assumed knowledge that I lack), I cannot comment. However, one doesn't need a model to know that low iodine compounded with high perchlorate is bad based on the literature and clever extrapolations of the epidemiologists on the SAB-PAP panel. My concern is the assumption that the 40-week gestation pregnant mother represents all of pregnancy when we know that all thyroid hormones change during different trimesters of pregnancy and the impact of insufficiency in early pregnancy may be more serious than later.

b) My concern here is neglecting the measurement of perchlorate in the water used to make formula for older infants. Also, it is not clear to me why there is an impact at day 7 in formula-fed infants. Wouldn't any contribution from mother have vanished by this time in light of the Vulsma et al. (1989) study.

c) As I am having much difficulty understanding and seeing the essence of each graph, I cannot comment here.

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Question 6. Empirical functions to predict thyroid hormone levels: The pregnancy model (but not the lactation/infant models) uses empirical functions to make urinary clearance of iodine and metabolic degradation of T3 dependent on the iodine ingestion level, in order to predict observed nonlinearity in the relationship between thyroid hormone levels and iodine intake. Does this use of empirical functions result in predicted outcomes or trends that are not plausible for serum thyroid hormones, particularly fT4?

Hugh A. Barton, Ph.D.

The use of the empirical functions, which are essential for obtaining reasonable fits to the existing data, is reasonable. The need for these functions may reflect limitations of the current model structure or the available data or both. Absent these functions the model does not perform as well, so the predictions would be more questionable.

Claude Emond, Ph.D.

Empirical function is a good alternative when we do not have more information about biological observations. During many situations, the model was described by using a table function that showed biological observations by using an empirical distribution. The result provides an approximation of the plausible observation of the parameters. During the simulation performed in the context of short exposure, such as 90 days, the result is acceptable. However, to simulate the impact of lifetime exposure, repetitive gestation, or acyclic lactation, I think it would be better to express variations of the parameters.

Dale Hattis, Ph.D.

I can't tell from the information I have available.

Angela M. Leung, M.D., M.Sc.

Comments regarding empirical functions in the pregnancy model:

The pregnancy model as reported in Lumen et al. (2013) (including Tables 2 and 3 and their corresponding text) was reviewed in relation to this question. The functions used in the pregnancy model regarding the urinary iodine clearance and metabolic degradation of T3 are supported by the trimester-specific calibration parameters used. The predicted outcomes and trends for serum FT4 concentrations, as presented in the pregnancy model, are plausible and in line with those reported for the high perchlorate exposure ("Taltal") group in the Tellez R et al. (2005) report.

Michael H. Lumpkin, Ph.D., DABT

The use of empirical relationships to describe urinary iodine clearance and T3 degradation does not, based on the model performance shown in the report, appear to result in implausible thyroid hormone levels.

Elizabeth N. Pearce, M.D., M.Sc.

Urinary clearance of iodine in pregnancy is largely a function of glomerular filtration rates since iodine is believed to be largely passively excreted at the kidney. The amount of ingested iodine will strongly influence the urinary iodine concentration, but not necessarily the fraction of plasma iodine which is renally excreted. Degradation of maternal T3 is strongly influenced by high levels of type 3 deiodinase in the placenta. I am not aware of data demonstrating that there are alterations in the placental DIO3 activity relative to differing iodine intakes. Therefore, although the empirical functions help to fit the model to observed data, they are not necessarily in line with currently understood physiology. The need to make these empiric adjustments to the model suggests data gaps which are worth exploring through future studies.

Stephen M. Roberts, Ph.D.

I will defer to other panel members on this charge question.

Joanne F. Rovet, Ph.D.

I cannot comment although the findings presented in the two Lumen et al. (2013, 2015) papers seem clearer and more robust to me than the current.

Question 7. Characterization of model predictions: The pregnancy and infant/lactation models were developed to specifically consider the range of iodine ingestion and thyroidal uptake where TSH is expected to stay in its normal range (i.e., they do not account for HPT feedback control). Do the models represent a reasonable effort to describe the relationships between iodine intake, perchlorate exposure and thyroid function? Are they sufficiently specific to predict perchlorate-induced changes in thyroid hormones in these life-stages over the range indicated? Please characterize the robustness, precision and sensitivity of the models for the ability to extrapolate changes in T4 associated with perchlorate exposures over the range from low exposures (less than 1 μg/kg/d) to higher levels which the model and analysis predict to be hypothyroxinemic.

Hugh A. Barton, Ph.D.

As noted in the general comments, this is a systems model of substantial complexity that appears to have been reasonably developed based upon available scientific information. Absent working with the models to develop a detailed understanding of their behavior, I would not try to comment on robustness, precision, or sensitivity for predictions. One substantial challenge of trying to characterize how well the model capture existing data and how good the predictions are is that there is substantial population variability in all the available data. The model really is a model of an individual that is evaluated against data assuming different levels of iodine intake. Further, as noted by a peer reviewer at the meeting, even in areas of general iodine insufficiency, many individuals are euthyroid so this model is essentially representing the subset of the population who show decreased T4 levels under those conditions and are among the sensitive members of the population. This makes comparisons to model outputs to available data, particularly implementation of explicit statistical fitting methods, a challenge. While such

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statistical fitting could provide much better perspective on the uncertainty in the model predictions, it may be very challenging to appropriately apply such methods across the range of data available.

Claude Emond, Ph.D.

The models represent a reasonable effort, and the authors have provided detailed descriptions.

I believe these are good models (PBPK model women-fetus and women-infant) because it describes the major step of the mode of action of the hypothyroxinemic by using recent literature. I believe that this PBPK model reached the maximum of its potential based on the literature available and referenced, and can be used along with the exposure observation inside the range it was established or limited. I believe that this model will further improve and become more sophisticated when more information about biological observations are included. We need to remember that a model is a simplification of biological observations. We will probably never be able to describe in the close future all of the biological mechanism processes implicated in hypothyroxinemic; however, this PBPK model can include the major pieces of limiting step in the sequential mode of action causing this effect. Here, in this model, only the effect of a supplement of iodine and the exposure of perchlorate are considered in inducing hypothyroidism; nevertheless, other physiological disturbances may also cause the issue. In addition, this model predicts the range specified by the authors. In the future, the PBPK models will need to be challenged to characterize exposure situation out of the range mentioned in the report, to gain a better understanding about the limitation of each parameter implicated in the PBPK model, and to study the impact of this model on the fetus. Specifically, the fetus might be sensitive to perchlorate, but there is not enough information to conduct a simulation like we did for infants and women.

Dale Hattis, Ph.D.

Without the improved model performance tests on calibration I have described earlier, I cannot quantitatively evaluate the accuracy of the model predictions. The modes are "sufficiently specific to predict perchlorate-induced changes in thyroid hormones in these lifestages". How accurate the predictions are is anyone's guess.

Angela M. Leung, M.D., M.Sc.

Comments regarding characterization of model predictions:

The current model and sub-models are based on the assumption that the range of perchlorate exposure doses and iodine intake levels studied would be autoregulated by the thyroid to compensate for these perturbations, and thus only serum thyroxine levels are decreased while serum TSH concentrations remain normal (i.e., hypothyroxinemia is the primary endpoint). The model attempts to describe the relationships between iodine intake, perchlorate exposure, and serum thyroid function, but may be significantly influenced by the following major limitations, as has been described in greater detail in my previous comments:

- Serum thyroid hormone concentrations in pregnancy cannot be reliably extrapolated for lactation.

- Lack of serum thyroid autoantibody data, which may impact serum thyroid hormone concentrations and reference ranges.
- Variation in breastmilk iodine content in relation to recent dietary iodine ingestion.
- Calibration of the model for many crucial parameters (iodine and concentrations in breastmilk, maternal urine, and infant urine, and for infant serum thyroid function) was based on the study by Leung 2012, which did not examine women who were exclusively breastfeeding. Thus, the iodine nutrition provided to their infants was derived from a combination of both breastmilk and infant formula.
- The effects of likely coexposures from other NIS inhibitors on breastmilk and urinary iodine and perchlorate concentrations, and or infant serum thyroid function, are not addressed.

Michael H. Lumpkin, Ph.D., DABT

The model performance across the various represented life stages appears to be robust for low perchlorate exposures and iodide intake levels resulting in thyroid hormone levels above the 10th percentiles for the reference ranges. Although the model is restricted to represent limited thyroid hormone homeostasis in isolation of HPT feedback mechanisms (and, possibly, compensatory corrections of iodide uptake and transport inhibition), it represents a plausible and technically justified approach to defining the perchlorate dose-response across a narrow exposure range. Given the model's isolation from the HPT feedback mechanisms, there may be increased uncertainty in the dose-response curves as they approach the hypothyroxinemia/hypothyroidism threshold, defined herein at the 2.5th percentile of fT4 levels. It is doubtful that TSH expression occurs in an "all or nothing" response immediately at T4 levels below the 2.5th percentile. I believe that suggested inclusion of 1st trimester gestation into the model and subsequent simulations of epidemiological cohort data sets involving relatively high perchlorate exposures would be very helpful in identifying whether the profile of the BBDR's dose-response curves in the region of hypothyroxinemia can be adequately predicted without input from compensatory mechanisms.

Elizabeth N. Pearce, M.D., M.Sc.

As noted above, I believe that the lack of consideration of the HPT axis in the BBDR model is a very substantial limitation of the model and limits its biological plausibility. Effects of NIS inhibition on free T4 cannot necessarily be fully understood without factoring in compensatory processes. In addition, effects of TSH on the T3:T4 ratio might have deleterious effects for fetal hypothyroxinemia which cannot be appreciated without inclusion of the HPT axis in models. I would strongly favor expanding models to include the HPT axis (recognizing that this does add a substantial degree of complexity).

I would also favor eliminating consideration of maternal hypothyroxinemia as a primary outcome for the lactating women. Lactating women would still need to be modeled in order to estimate the amounts of breast milk iodine and perchlorate exposure to inform the model of free T4 in breastfed infants.

I would recommend expanding the pregnancy model to include the first and second trimesters, the gestational ages for which there are currently epidemiologic data to demonstrating adverse developmental effects of maternal hypothyroxinemia. Modeling the fetus at this stage is far less critical than modeling the pregnant woman herself, sine associations with development outcomes are currently known relative to maternal, but not fetal, thyroid function.

I would expand the literature search and use new data to further calibrate the expanded models.

Stephen M. Roberts, Ph.D.

The models make a reasonable effort to focus on a range of fT4 levels that is of concern from the standpoint of potential neurodevelopmental effects, yet is not so low as to trigger increased TSH, which would complicate the modeling substantially. The models make a reasonable effort to describe the relationships between iodine intake, perchlorate exposure and thyroid function for the sensitive life stages of interest. The last portion of the charge question appears to be similar to the question posed in 3C, except focuses specifically on the T4 predictions. The response is the same — the robustness, precision, and sensitivity are difficult to gauge based upon the information presented in the report. In part, this is due to the nature of the limited data available for external validation of the model predictions.

Joanne F. Rovet, Ph.D.

I am not sure why HPT feedback control is not considered when TSH is to me a marker of brain sufficiency of thyroid hormone. Thus, I am less than enthusiastic of the quality of the current models for predicting T4 changes following the various perchlorate exposures. Figure 17, however, shows the importance of iodide sufficiency.

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V. SPECIFIC OBSERVATIONS ON MODEL REPORT

Hugh A. Barton, Ph.D.

Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
12	1-2	Is the wording here, "particularly sensitive" "strongly supported" too strong.
23	15-17	As noted in comments above, clarify this sentence about halting the review process.
24	8	Change "where" to "were"
33	10	Hematocrit is referred to here and several additional times, but the values used do not appear to be reported.
85		In Figures and Tables or report and appendix, some parameters have _SENS added to their names, but it wasn't entirely clear what this meant, e.g., why do some parameters have it and other don't?

Claude Emond, Ph.D.

No specific observations on Model Report provided.

Dale Hattis, Ph.D.

Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
--	--	**List of Abstracts of Papers that May Be Helpful in Quantitatively Estimating the Effects of Iodine and Thyroid Hormone Deficiency on IQ from Exposure During Early Pregnancy** 1. **Morreale de Escobar G, Obregón MJ, Escobar del Rey F. Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia? J. Clinical Endocrinology and Metabolism 85: 3975-3987.** **Abstract** Several recent publications have drawn attention to the role of the thyroid hormone status of the mother on the future neuropsychological development of the child. The screening of pregnant women for clinical or subclinical hypothyroidism based on second trimester elevated maternal TSH values has been proposed. **Here, we have summarized present epidemiological and experimental evidence strongly suggesting that conditions resulting in first trimester hypothyroxinemia (a low for gestational age circulating maternal free T_4, whether or not TSH is increased) pose an increased risk for poor neuropsychological development of the fetus.** This would be a consequence of decreased availability of maternal T_4 to the developing brain, its only source of thyroid hormone during the first trimester; T_4 is the required substrate for the ontogenically regulated generation of T_3 in the

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Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
		amounts needed for optimal development in different brain structures, both temporally and spatially. Normal maternal T_3 concentrations do not seem to prevent the potential damage of a low supply of T_4, although they might prevent an increase in circulating TSH and detection of the hypothyroxinemia if only TSH is measured. Hypothyroxinemia seems to be much more frequent in pregnant women than either clinical or subclinical hypothyroidism and autoimmune thyroid disease, especially in regions where the iodine intake of the pregnant woman is inadequate to meet her increased needs for T_4. It is proposed that the screening of pregnant women for thyroid disorders should include the determination of free T_4 as soon as possible during the first trimester as a major test, because hypothyroxinemia has been related to poor developmental outcome, irrespective of the presence of high titers of thyroid autoantibodies or elevated serum TSH. The frequency with which this may occur is probably 150 times or more that of congenital hypothyroidism, for which successful screening programs have been instituted in many countries. - See more at: http://press.endocrine.org/doi/abs/10.1210/jcem.85.11.6961#sthash.MBJebpGn.dpuf 2. **Cao XY, Jiang XM, Dou ZH, Rakeman MA, Zhang ML, O'Donnel K, Ma T, Amette K, DeLong N, Delong GR. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med. 1994 Dec 29;331(26):1739-44.** **Abstract** **BACKGROUND:** Endemic cretinism, caused by severe iodine deficiency during pregnancy, is the world's most common preventable cause of mental retardation. It can be prevented by iodine treatment before conception, but whether it can be prevented or ameliorated by treatment during pregnancy or after delivery is not known. **METHODS:** In a severely iodine-deficient area of the Xinjiang region of China, we systematically administered iodine to groups of children from birth to three years of age (n = 689) and women at each trimester of pregnancy (n = 295); we then followed the treated children and the babies born to the treated women for two years. We used three independent measures of neural development: the results of the neurologic examination, the head circumference (which correlates with brain weight in the first postnatal year), and indexes of cognitive and motor development. Untreated children one to three years of age, who were studied when first seen, served as control subjects.

		RESULTS: The prevalence of moderate or severe neurologic abnormalities among the 120 infants whose mothers received iodine in the first or second trimester was 2 percent, as compared with 9 percent among the 752 infants who received iodine during the third trimester (through the treatment of their mothers) or after birth (P = 0.008). The prevalence of microcephaly (defined as a head circumference more than 3 SD below U.S. norms) decreased from 27 percent in the untreated children to 11 percent in the treated children (P = 0.006), and the mean (+/- SD) developmental quotient at two years of age increased (90 +/- 14, vs. 75 +/- 18 in the untreated children; P < 0.001). Treatment in the third trimester of pregnancy or after delivery did not improve neurologic status, but head growth and developmental quotients improved slightly. Treatment during the first trimester, which was technically problematic, improved the neurologic outcome. **CONCLUSIONS:** Up to the end of the second trimester, iodine treatment protects the fetal brain from the effects of iodine deficiency. Treatment later in pregnancy or after delivery may improve brain growth and developmental achievement slightly, but it does not improve neurologic status. **Comment in** Iodine deficiency and fetal brain damage. [N Engl J Med. 1994] 3. **Gilbert M, Rovet J, Chen Z, Koibuchi N. Developmental thyroid hormone disruption: Prevalence, environmental contaminants and neurodevelopmental consequences, Neurotoxicology, Volume 33 (2012) 842-852.** **Abstract** Thyroid hormones (TH) are critical for growth and development and particularly brain development. There are numerous environmental agents that lead to marginal reductions of circulating TH. Although it is clear that severe developmental hypothyroidism is profoundly detrimental to neurodevelopment, there is less information regarding the consequences of modest degrees of thyroid. The impact of low level TH disruptions induced by environmental contaminants has not been defined. This paper is a synopsis from four invited speakers who presented at the 13th International Neurotoxicology Association meeting held in Xi'an, China during the summer of 2011. An overview of the role of TH in brain development and a review of human and animal data on the neurological sequelae of disruption of the thyroid axis in the pre- and early post-natal periods were presented by Mary Gilbert and Joanne Rovet. Iodine deficiency, a common cause of TH insufficiency and mental retardation in many countries, including China, was addressed by Zupei Chen. In this presentation the current incidence of iodine deficiency and neurological outcome in China and the efficacy of recently implemented iodinization programs to eliminate this cause of mental

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		retardation were reviewed. Joanne Rovet described the impact of TH disruption during pregnancy and under conditions of congenital hypothyroidism. Children born with normal thyroid function, but who experienced TH insufficiency in the womb, display subtle cognitive impairments and abnormalities in brain imaging. Despite early detection and treatment, deficiencies also exist in children born with thyroid disorders. Different patterns of cognitive effects result from prenatal versus postnatal TH insufficiency. Mary Gilbert reported on the effects of environmental contaminants with thyroid disrupting action on brain development in animals. Results of neurophysiological, behavioral, structural and molecular alterations that accompany modest perturbations of the thyroid axis were reviewed. Noriyuki Koibuchi described molecular targets of TH-mediated signaling accompanying exposure to persistent organic pollutants. Both polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are prevalent environmental contaminants that disrupt TH signaling at the receptor level. This action by these chemical classes could contribute to the negative impact of these chemicals on brain function. In summary, epidemiological, preclinical and animal research has clearly identified the critical role of TH in brain development. Additional work is required to understand the impact of low level perturbations of the thyroid axis to evaluate the risk associated with environmental contaminants with thyroid action. 4. **Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice R, Channon S, Braverman LE, Dayan CM, Lazarus JH, Pearce EN. Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the Controlled Antenatal Thyroid Study. **J Clin Endocrinol Metab. 2014 Nov;99(11):4291-8. doi: 10.1210/jc.2014-1901. Epub 2014 Jul 24.** **Abstract** **OBJECTIVE:** Thyroid dysfunction is associated with impaired cognitive development. Perchlorate decreases thyroidal iodine uptake, potentially reducing thyroid hormone production. It is unclear whether perchlorate exposure in early life affects neurodevelopment. **DESIGN:** Historical cohort analysis. **PATIENTS:** From 2002 to 2006, 21,846 women at gestational age <16 weeks recruited from antenatal clinics in Cardiff, UK and Turin, Italy were enrolled in the

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		Controlled Antenatal Thyroid Screening Study (CATS). We undertook a retrospective analysis of 487 mother-child pairs in mothers who were hypothyroid/hypothyroxinemic during pregnancy and analyzed whether first trimester maternal perchlorate levels in the highest 10% of the study population were associated with increased odds of offspring IQ being in the lowest 10% at 3 years of age. **MAIN OUTCOME MEASURES:** Maternal urinary perchlorate, offspring IQ. **RESULTS:** Urine perchlorate was detectable in all women (median 2.58 μg/L); iodine levels were low (median 72 μg/L). **Maternal perchlorate levels in the highest 10% of the population increased the odds of offspring IQ being in the lowest 10% OR = 3.14 (95% CI 1.38, 7.13) P = .006 with a greater negative impact observed on verbal OR = 3.14 (95% CI 1.42, 6.90) P = .005 than performance IQ. Maternal levothyroxine therapy did not reduce the negative impact of perchlorate on offspring IQ.** **CONCLUSIONS:** This is the first study using individual-level patient data to study maternal perchlorate exposure and offspring neurodevelopment and suggests that high-end maternal perchlorate levels in hypothyroid/hypothyroxinemic pregnant women have an adverse effect on offspring cognitive development, not affected by maternal levothyroxine therapy. These results require replication in additional studies, including in the euthyroid population. **Comment in** • Perchlorate exposure in pregnancy and cognitive outcomes in children: it's not your mother's thyroid. [J Clin Endocrinol Metab. 2014] PMID: 25057878 DOI: 10.1210/jc.2014-1901[PubMed - indexed for MEDLINE] **5. Lain, SJ, Bentley, JP, Wiley, V, Roberts, CL, Jack, M, Wilcken, B., Nassar, N. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diabetes Endocrinol. 2016 Sep;4(9):756-65. doi: 10.1016/S2213-8587(16)30122-X. Epub 2016 Jul 22.** **Summary** **Background** Congenital hypothyroidism causes intellectual delay unless identified and effectively treated soon after birth. Newborn screening has almost eliminated

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		intellectual disability associated with congenital hypothyroidism. However, clinical uncertainty remains about infants with thyroid-stimulating hormone (TSH) concentrations less than the newborn screening cutoffs. We assessed the association between neonatal TSH concentrations and educational and developmental outcomes. **Methods** We did a population-based record-linkage study of all liveborn infants undergoing newborn screening from 1994 to 2008 in New South Wales, Australia, with assessments of childhood development or school performance. Very-low-birthweight babies (<1500 g) were excluded. Developmental and educational outcomes were obtained and these were linked to individual records by the New South Wales Centre for Health Record Linkage. The primary educational outcome was the proportion of students with National Assessment Program Literacy and Numeracy (NAPLAN) results lower than the national minimum standard in reading or numeracy measured at all ages, and the primary developmental outcome was the proportion of children who were classified as being developmentally high risk (vulnerable in two or more of the five developmental domains assessed by the Australian Early Development Census) at age 4–6 years. The proportions of infants with each outcome were calculated per percentile (0–100) of TSH concentration. Multivariable logistic regression was used to account for potential confounding by maternal and fetal variables known to affect neonatal TSH concentrations or neurodevelopmental outcomes. **Findings** 503 706 infants had a neonatal TSH result that linked to a developmental or educational outcome. 149 569 infants born between 2002 and 2008 were linked to an Australian Early Development Census developmental outcome and 354 137 were linked to a NAPLAN educational outcome. Median follow-up for educational outcome was 10 years (IQR 8–12) and for developmental outcome was 5 years (5–6). 5·5% (14 137 of 257 752) of infants with TSH concentrations lower than the 75th percentile scored less than the national minimum standard for numeracy, and this increased with each increase of percentile group to 11·3% (15 of 133) of infants with a TSH concentration between the 99·90th and 99·95th percentile. Infants with a neonatal TSH concentration in the 99·95th percentile or higher (above newborn screening cutoff) and likely to have diagnosed and treated congenital hypothyroidism had similar results to infants with a TSH concentration lower than the 75th percentile for both educational and developmental outcomes. Infants with a neonatal TSH concentration between the 99·5th and 99·9th percentile were more likely to have special needs (adjusted odds ratio [aOR] 1·68, 95% CI 1·23–2·30), poor numeracy performance (aOR 1·57, 1·29–1·90), and developmentally high risk (aOR 1·52, 1·20–1·93).

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		Interpretation We found an association between neonatal TSH concentrations lower than the present newborn screening thresholds and poor educational and developmental outcomes. This association needs further investigation to assess whether assessment and treatment of these infants might improve their long-term cognitive outcomes. **Funding** Australian National Health and Medical Research Council. 6. **Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC), Lancet. 2013 Jul 27;382(9889):331-7. doi: 10.1016/S0140-6736(13)60436-5. Epub 2013 May 22.** **Summary** **Background:** As a component of thyroid hormones, iodine is essential for fetal brain development. Although the UK has long been considered iodine replete, increasing evidence suggests that it might now be mildly iodine deficient. We assessed whether mild iodine deficiency during early pregnancy was associated with an adverse effect on child cognitive development. **Methods:** We analyzed mother–child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort by measuring urinary iodine concentration (and creatinine to correct for urine volume) in stored samples from 1040 first-trimester pregnant women. We selected women on the basis of a singleton pregnancy and availability of both a urine sample from the first trimester (defined as ≤13 weeks' gestation; median 10 weeks [IQR 9–12]) and a measure of intelligence quotient (IQ) in the offspring at age 8 years. Women's results for iodine-to-creatinine ratio were dichotomised to less than 150 μg/g or 150 μg/g or more on the basis of WHO criteria for iodine deficiency or sufficiency in pregnancy. We assessed the association between maternal iodine status and child IQ at age 8 years and reading ability at age 9 years. We included 21 socioeconomic, parental, and child factors as confounders. **Findings:** The group was classified as having mild-to-moderate iodine deficiency on the basis of a median urinary iodine concentration of 91·1 μg/L (IQR 53·8–143; iodine-to-creatinine ratio 110 μg/g, IQR 74–170). After adjustment for confounders, children of women with an iodine-to-creatinine ratio of less than 150 μg/g were more likely to have scores in the

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		lowest quartile for verbal IQ (odds ratio 1·58, 95% CI 1·09–2·30; p=0·02), reading accuracy (1·69, 1·15–2·49; p=0·007), and reading comprehension (1·54, 1·06–2·23; p=0·02) than were those of mothers with ratios of 150 µg/g or more. When the less than 150 µg/g group was subdivided, scores worsened ongoing from 150 µg/g or more, to 50–150 µg/g, to less than 50 µg/g. **Interpretation:** Our results show the importance of adequate iodine status during early gestation and emphasize the risk that iodine deficiency can pose to the developing infant, even in a country classified as only mildly iodine deficient. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention. 7. **Min H, Dong J, Wang Y. et al. Maternal Hypothyroxinemia-Induced Neurodevelopmental Impairments in the Progeny. Molecular Neurobiology 53(3): 1613-1624.** **Abstract** Maternal hypothyroxinemia can induce neurodevelopmental impairments in the developing fetus. We here review recent studies on the epidemiology and molecular mechanisms associated with this important public health issue. In 2011, the American Thyroid Association defined maternal hypothyroxinemia as low serum free thyroxine (FT4) levels (<5th or <10th percentile) existing in conjunction with normal serum free triiodothyronine (FT3) or thyroid stimulating hormone (TSH) levels during pregnancy. Compared to clinical or subclinical hypothyroidism, hypothyroxinemia is more commonly found in pregnant women. Hypothyroxinemia usually ensues in response to several factors, such as mild iodine deficiency, environmental endocrine disrupters, or certain thyroid diseases. Unequivocal evidence demonstrates that maternal hypothyroxinemia leads to negative effects on fetal brain development, increasing the risks for cognitive deficits and poor psychomotor development in resulting progeny. In support of this, rodent models provide direct evidence of neurodevelopmental damage induced by maternal hypothyroxinemia, including dendritic and axonal growth limitation, neural abnormal location, and synaptic function alteration. The neurodevelopmental impairments induced by hypothyroxinemia suggest an independent role of T4. Increasing evidence indicates that adequate thyroxine is required for the mothers in order to protect against the abnormal brain development in their progeny. 8. **Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe, VWV, B de Rijke, Y, Steegers, EA, Visser TJ, White T, Tiemeier H, Peeters RP. Association of maternal thyroid function during early pregnancy with off spring IQ and brain morphology in**

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		childhood: a population-based prospective cohort study. The Lancet Diabetes-Endocrinology 2016 4:35-43. **Background** Thyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology. **Methods** In this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine. **Findings** Data for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).

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		Interpretation Both low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results. 9. **Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice R, Channon S, Braverman LE, Dayan CM, Lazarus JH, Pearce EN. Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the Controlled Antenatal Thyroid Study. J Clin Endocrinol Metab 2014 Nov;99(11):4291-8. doi: 10.1210/jc.2014-1901. Epub 2014 Jul 24.** **Objective:** Thyroid dysfunction is associated with impaired cognitive development. Perchlorate decreases thyroidal iodine uptake, potentially reducing thyroid hormone production. It is unclear whether perchlorate exposure in early life affects neurodevelopment. **Design:** Historical cohort analysis. **Patients:** From 2002 to 2006, 21,846 women at gestational age <16 weeks recruited from antenatal clinics in Cardiff, UK and Turin, Italy were enrolled in the Controlled Antenatal Thyroid Screening Study (CATS). We undertook a retrospective analysis of 487 mother-child pairs in mothers who were hypothyroid/hypothyroxinemic during pregnancy and analyzed whether first trimester maternal perchlorate levels in the highest 10% of the study population were associated with increased odds of offspring IQ being in the lowest 10% at 3 years of age. Main Outcome Measures: Maternal urinary perchlorate, offspring IQ. **Results:** Urine perchlorate was detectable in all women (median 2.58 µg/L); iodine levels were low (median 72 µg/L). Maternal perchlorate levels in the highest 10% of the population increased the odds of offspring IQ being in the lowest 10% OR=3.14 (95% CI 1.38, 7.13) P=.006 with a greater negative impact observed on verbal OR=3.14 (95% CI 1.42, 6.90) P=.005 than performance IQ. Maternal levothyroxine therapy did not reduce the negative impact of perchlorate on offspring IQ.

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		Conclusions: This is the first study using individual-level patient data to study maternal perchlorate exposure and offspring neurodevelopment and suggests that high-end maternal perchlorate levels in hypothyroid/hypothyroxinemic pregnant women have an adverse effect on offspring cognitive development, not affected by maternal levothyroxine therapy. These results require replication in additional studies, including in the euthyroid population. (J ClinEndocrinolMetab 99: 4291–4298, 2014)
6	5-16	This risks missing possibly the most serious effects on IQ for pregnant women in the lowest range of iodide intake. This may not control RfD selection, but may well be very important for estimating overall IQ effects and therefore juxtaposing costs and benefits of alternative choices of RfDs and measures to reduce perchlorate exposures.
6	18-21	Could be a substantial limitation.
7	2-8	Critically evaluate this evidence supporting model calibration.
7	9-16	These ranges of iodide intake seem unduly restricted—support with reference to actual US iodide intake and excretion information from NHANES.
7	17-25	Having "reference intervals" as the touchstone of the analysis is distinctly suboptimal for juxtaposing relative costs and benefits of regulatory options. Much better would be to make predictions of IQ effects which can be economically valued and juxtaposed with estimates of economic costs.
7	26-32 33-36 Footn ote 2	What? No analysis of variability and uncertainty in this parameter (refers to "the revised value" implying no distributional treatment for what is stated to be a key component of the analysis). Variability—why is it assumed that everyone is the same in this? Uncertainty—surely the value has not been determined to a precision where the implications of uncertainty need not be analyzed.
8	15-20	Analysis by "reference range" is likely to be misguided. Changes within the reference range may still be associated with harm. This focus on reference ranges and the lack of data for potentially the most vulnerable segment of the population is an additional reason to treat the modeling results with considerable caution in judging appropriate exposure control standards.
9	6-13	This clearly requires quantitative assessment of the effects of exposure changes for the entire population, not just the segments for which a "reference range" is available. The effects of interest include prominently those on IQ, for which it would be possible to juxtapose quantifiable economic benefits with quantifiable economic costs. And the analysis must clearly include the full range of iodine intakes in the real US population, as best it can be estimated from available data.

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11	1-13	These references must be systematically evaluated in order to convert the analysis to implications for IQ changes rather than just "hypothyroxinemia." Such conversion is essential for a reasonable juxtaposition of costs and benefits of regulatory alternatives. The abstract for the most recent Min et al. (2016) is: Molecular Neurobiology April 2016, Volume 53, Issue 3, pp 1613–1624 Maternal Hypothyroxinemia-Induced Neurodevelopmental Impairments in the Progeny • Authors Authors and affiliations • Hui Min, Jing Dong, Yi Wang, Yuan Wang, Weiping Teng, Qi Xi. 2016. • Hui Min[1][2] • Jing Dong[1][2] • Yi Wang[1][2] • Yuan Wang[1][2] • Weiping Teng[2] • Qi Xi[3] Email author • Jie Chen[1][2] Email author 1. Department of Occupational and Environmental Health, School of Public HealthChina Medical UniversityShenyangPeople's Republic of China 2. Liaoning Provincial Key Laboratory of Endocrine DiseasesThe First Hospital of China Medical UniversityShenyangPeople's Republic of China 3. Department of PhysiologyThe University of Tennessee Health Science CenterMemphisUSA Article **First Online:** 11 February 2015 **DOI**: 10.1007/s12035-015-9101-x **Cite this article as:**
12-13	--	Need to add to Schlosser document reference to biphasic relationship between fT4 during pregnancy and childhood nonverbal IQ measures and brain size measures. This would allow reframing of measures of TH perturbation to measures of IQ directly relatable to serious economic and other consequences as a function of iodide intake distributions.
14	--	Model should clearly be extended to cover effects during early pregnancy where T4 deficiency is likely to have the greatest effects on neurodevelopment.

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16	footnote	[3] Here we use "reference range" to refer to the range of a hormone that is considered normal and healthy for a population. Hence some in the population will have hormone levels above or below that reference range and be identified as having an adverse clinical condition. The "population distribution" refers to the distribution of hormone levels in the entire population, including those outside of the reference range. [4] The model does not describe TSH levels, but assumes they stay within the normal reference range. Clinically, significant elevations in TSH can be observed whether or not T4 of fT4 are in the reference range. Thus there are not specific levels of T4/fT4 that are definitively associated with TSH elevation. This may be due to inter-individual variability in hormonal control mechanisms. But mechanistically it is known that TSH production and release are stimulated by decreasing T4 levels. Hence for the purpose of this model, specific, life-stage-specific fT4 levels are identified below which TSH levels are expected to be sufficiently stimulated as to rise above their reference range and introduce significant feedback control on the thyroid, which would make model predictions invalid.
17	12-21	There is no apparent justification for drawing the line at the 2.5th percentile. This is pretty important because it may be that later the authors essentially ignore possible effects outside this limit, thus potentially biasing the analysis by excluding an especially sensitive segment of the population.
17	22-24	I think this is a problem for the analysis—levels of iodide intake below this are present in the US population (analyze NHANES data) and likely represent a sensitive subgroup that could affect expected IQ benefits of perchlorate exposure reduction.
18	2-13	
18	14-25	There is a grave danger here of understating perchlorate hazard and benefits of exposure reduction. The analysis should consider the effects of perchlorate for the full range and frequency of iodide exposures in the U.S. population. Otherwise both the baseline amount of harm from current perchlorate exposures and the benefits and costs of changes in those exposures will be mis-analyzed. (give fuller analysis of this distribution here?)
20	8-15	More explanation is needed for the choice of this distribution. Why not use a lognormal? Data should be shown to indicate that a normal or lognormal does not fit, if that is true. See analysis of the data in App-25 below.
44	22-24	The single-value for this binding constant has been changed more than 2-fold from the earlier value. Yet there is no allowance for either variability or uncertainty. This should be improved in subsequent analyses to at least provide some sensitivity analysis for both uncertainty and variability. Analyze in detail.
45	1-23	
45	9-16	Overall this conclusory presentation leaves much to be desired. Comparisons to the data fits before and after revision should be provided to allow a meaningful review.

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45	17-23	This certainly suggests that something may be amiss in the basic calibration of the model. It is reassuring that the author does not think that key predictions in the current analysis are not affected much, but because other uses of the model are expected in the future, this issue may well need to be revisited.
46	2-12	
60	10-19	This is completely unconvincing. The figure referred to has an enormous amount of scatter, even with the data points plotted on a logarithmic y-axis. To then say, given this scatter, that "the model-predicted urinary iodide concentrations…were within the range of literature-reported values (Figure 4) really is such a loose standard that it seems hardly meaningful. Minimally, there needs to be some statistical summarization of the comparison data and some specific comparison of the summary data with a specific set of model predictions.
61	6-12	The comparison depicted in the bottom panel is also unconvincing, lacking any statistical summarization to help the reader judge whether the comparison supports or refutes the predictions of the model.
63	10-17	Similarly, the conclusion from Figure 6 that the predicted perchlorate concentrations are "within the range of reported values" is completely unconvincing. What is shown in Figure 6 is a plot of highly scattered observations plotted over a four order of magnitude range with no statistical summarization of the data to allow reasonable juxtaposition of the central tendency and uncertainty range of the observations with corresponding model expectations.
64	9-13	The lack of correspondence of the data points to model predictions is unsettling. And the proffered explanation "that iodide levels are not stable in breast-milk samples" is no help. Instability would be expected to lead to scatter of the data points, but not a systematic bias lowering the data points relative to model expectations. The modelers' response in this case makes no sense.
67	11-12	As indicated by my remarks above, I disagree. The authors should develop a range of alternative models that would fit these data as well or better based on much more rigorous criteria than that the models produce results "within the range" of the observations presented on multi-order-of magnitude plots. They should then document the implications of the alternative models for the effect of various levels of perchlorate on range of policy-relevant parameter values such as IQ distributions.
69	7-12	Although the authors seem to be following SAB advice in this choice of criteria for defining adversity, I think it would be much better to use-IQ change criteria based on recently available information. Making IQ change the focus of the analysis can build upon the modeling work done so far, but yield results in terms that can be valued economically and juxtaposed much more readily with costs of alternative measures to reduce perchlorate exposures. This corresponds much more closely to the mandate for analysis

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		under the Safe Drinking Water Act, as I understand it and described in the introductory sections of the model report.
70	11-14	There should be an analysis of the effects of a plausible uncertainty range for this parameter, given that it has been appreciably changed from what was assumed in prior modeling. The authors may also wish to explore the potential consequences of variability among people in the values of this key parameter, particularly if a literature search yields evidence of a polymorphism in the gene related to this binding constant. At the very least, there should be some discussion of the possibility that this gene may be polymorphic.
71	3-6	Surely the model results are uncertain both above and below the indicated level. Perhaps they are more uncertain below 10.6 ppm but the criterion indicated cannot indicate a sharp cutoff where uncertainty starts.

Angela M. Leung, M.D., M.Sc.

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Throughout	--	Suggest replacing the term "bottle-fed" with "formula-fed" throughout the report and its figures. Currently, both are used interchangeably, and thus it should be clarified that the contents of the infant bottle are referring to only infant formula, rather than breastmilk or a combination of both.
8	10	Suggest deleting "medically"
16	Footnote 4	• Suggest clarifying the first sentence by inserting "serum" before TSH. • The second sentence would be better rephrased by deleting the word "Clinically". • There is typo in the second sentence: "T4 or FT4" levels The 4th and 5th sentences should be combined and can be better rephrased as: "This may be due to inter-individual variability in hormonal control mechanisms, but TSH is generally stimulated by decreasing T4 levels."
16	4	The word "both" here may be confusing with this sentence structure – consider deleting.
16	8	The HPT axis should be assumed to be intact in all individuals, which this sentence suggests again. Recommend replacing the phrase "involved with regulating thyroid hormone concentrations" with "perturbed".
16	14	Recommend deleting "just"
17	3	Should be "conditions"
17	8	Suggest replacing "Elevated TSH levels" with "Elevated serum TSH concentrations"
17	13-14	Suggest replacing "euthyroid conditions occur for" with "euthyroidism

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		is defined as", and "hypothyroxinemia occurs for" with "hypothyroxinemia is defined as"
17	20-21	Typos in this sentence with the missing end parentheses and double period.
18	19	Note that the recommended iodine intake for lactating women of 250 mcg/day is that by the WHO, UNICEF, and ICCIDD (now IGN), but the U.S. Institute of Medicine has a slightly different recommendation of 290 mcg/day for lactating women.
20	1	Insert: "For the formula-fed infant, the age-specific mean fT4 concentration was defined…"
21	Table 1	• The units of FT4 should be included. • It should be clarified that these are serum FT4 concentrations. It is customary to use the term "full-term" rather than "normal-term" infants.
32	Figure 3	The arrow terminating in "infant ingestion" may be misleading to some and can be better redrawn to clarify that this is not resulting in the set of processes immediately below this (i.e. thyroid plasma refers to the mother, not the infant).
37	6	It can also be cited that the placenta strongly expresses the type III deiodinase (Roti et al; PMID 7263836), thus partially responsible for the high rT3 levels seen at birth.
61	3	Typo: Should be cow milk-based formula
61	6-12	Suggest use of the term "urinary perchlorate concentrations" throughout this paragraph to minimize potential confusion
80	14	The subscript #11 appears to be a typo and can be deleted

Michael H. Lumpkin, Ph.D., DABT

No specific observations on Model Report provided.

Elizabeth N. Pearce, M.D., M.Sc.

Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
6	20	"thyroid hormone excretion" would be better worded as "thyroid hormone synthesis and secretion"
16	Footnote 4	"mechanistically it is known that TSH production and release are stimulated by decreasing T4 levels": it is primarily decreased T3 (converted locally from T4 by type 2 deiodinase), that provides feedback at the pituitary and hypothalamus
18	1-3	"The pregnancy model was primarily developed and calibrated using an assumed iodine intake of 200 mcg/d, the level recommended for pregnant women": The Institute of Medicine's RDA for pregnancy is 220 mcg daily. The WHO recommends 250 mcg (WHO Secretariat,

Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
		Andersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr. 2007;10(12A):1606-11).
18	19-20	"The lactating mother model was primarily calibrated or tuned assuming iodine ingestion of 250 mcg/d, the level recommended for breast-feeding women.": The Institute of Medicine's RDA for lactation is 290 mcg daily. WHO recommends 250 mcg.
33	12	It is noted that infant plasma volume was calculated based on a study with an n of only 4. Are there more robust data available?
47	Table 6	It is unclear to me why the estimated body weight for lactating women would start out higher (74.6 kg) than that for women in the late third trimester of pregnancy (72.3 kg).
64 and 82		It is noted, per a personal communication from Ben Blount that iodine levels decrease with storage time of breast milk samples. This simply does not make sense if measurement techniques are adequate. There could be some degradation of matrices which might affect iodine measurements by some methods, but the iodine can't actually leave the sample.

Stephen M. Roberts, Ph.D.

Significant observations and comment on the document are provided in the responses to charge questions above.

Joanne F. Rovet, Ph.D.

Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
1		Title is not accurate re "pregnant mother and fetus"
6	20-21	This assumption is not clear to me and I don't agree with it
7	13-14	This was confusing to me
7	27	Grammar – "which" describing wrong referent
8	1-3	Where is the evidence for this?
8	4-5	Where is the evidence for this?
8	15-18	What is the relevance of this statement
8	19	Wouldn't data from preterm cohorts suffice here?
11	15	Add "respectively" after "(hypothyroxinemia)"
12	1-2	I think this conclusion is out of context; it was meant infants versus grown men
12	5-7	I disagree – the real reason for suggesting greater sensitivity of infants than older children was the knowledge that the developing

Specific Observations on Model Report		
Page	***Line***	***Comment or Question***
		brain had a greater need for thyroid hormone at this earlier age
13	7	Why lactating mothers?
13	23	7-90 days is not the *most sensitive* period of thyroid function maturation; clearly gestational thyroid-hormone deficiency also has a major impact, particularly on behavior and vulnerability to later mental health issues
17	15	I am not happy with defining hypothyroxinemia for fT4 from 2.5-10th percentiles; Most studies are at least below 5th percentile. This is a statistical decision for studying effects, not a clinical condition
19	21-22	I don't understand this
20	8-11	Too technical
20	16-22	Please cite proper evidence
21	4	Remove "for example" - repeated
42	14	Add "in" before "umen"
43	4-5	Where does this idea come from – not sure it is true
43	5-6	Why? Where?
43	8-9	Why?
43	14	Comma after T3
43	14-15	Why?
44	5-6	Remove brackets around "McLanahan
44	6	"(see also U.S. EPA, 2009)
60	2	Perhaps cite Figure numbers in brackets
60	9	On what basis? Too vague.
60	16-22	Long sentence, hard to read
66	10-13	Confusing
67	11	Vague – what do you mean by "considered adequate"
70	11-13	Also Figure 10: where do these data come from?
77		Figure 14 Right – what is meant by "maternal iodine: 75 μg/d)"? Is this relevant?
78	8	Comma after "100 μg/L"
78	7-10	Long sentence, difficult to follow; not sure how you draw conclusion in sentence – where is the data
79	15	Where do reference values for fT4 come from
80	5-6	Not clear
80	14	"11": Actually, the Vulsma paper predict ~40%
80	11-13	Where are the data in Leung et al. (2012)? Did she provide the authors with the raw data as they only report correlational results?
83	11	Replace "birth" with "day 7"
84	1-3	Where are these data?

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VI. SPECIFIC OBSERVATIONS ON MODEL APPENDICES

Hugh A. Barton, Ph.D.

No specific observations on Model Appendices provided.

Claude Emond, Ph.D.

No specific observations on Model Appendices provided.

Dale Hattis, Ph.D.

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***
App-11	7-10	The fit in figure B-5 is clearly improved over the one that simply went through the lowest point. However the fit should be by inverse-variance weighted least squares not informal choose a value and evaluate fit by eye.
App-12	40-42	Why not assume an actual estimate of either national average or local perchlorate water and food exposures in the area where Greer et al. drew their subjects?
App-24 and -25		There is no specific analysis of the assembled data to evaluate the fit of simpler normal or lognormal distributions to the different observations and justify the use of the more complex lambda sigma model, which has one more parameter than a lognormal. I generated the following for simple normal and lognormal distributions for selected data sets with the most complete descriptions of the information. Overall, lognormal distributions seem to provide adequate fits, and although normal distributions provide a marginally better fit in a few specific cases, there is one case (Wang et al. first trimester) where the normal distribution falls conspicuously short in the fit as measured by the R squared statistic. I doubt that an Akaike information criterion test would find that the extra parameter needed for the lambda sigma distribution model would be justified.

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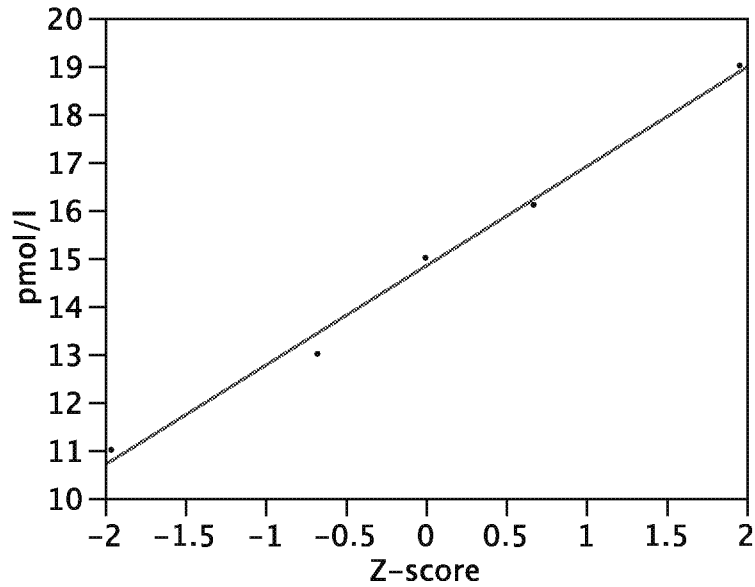
Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***
App-24 and -25		**Gong and Hoffman (2008) 1st trimester: Normal Distribution Fit**



Linear Fit
pmol/l = 14.82 + 2.068086*Z-score

Summary of Fit

RSquare	0.991989
RSquare Adj	0.989318
Root Mean Square Error	0.314541
Mean of Response	14.82
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	14.82	0.140667	105.36	<.0001
Z-score	2.068086	0.107303	19.27	0.0003

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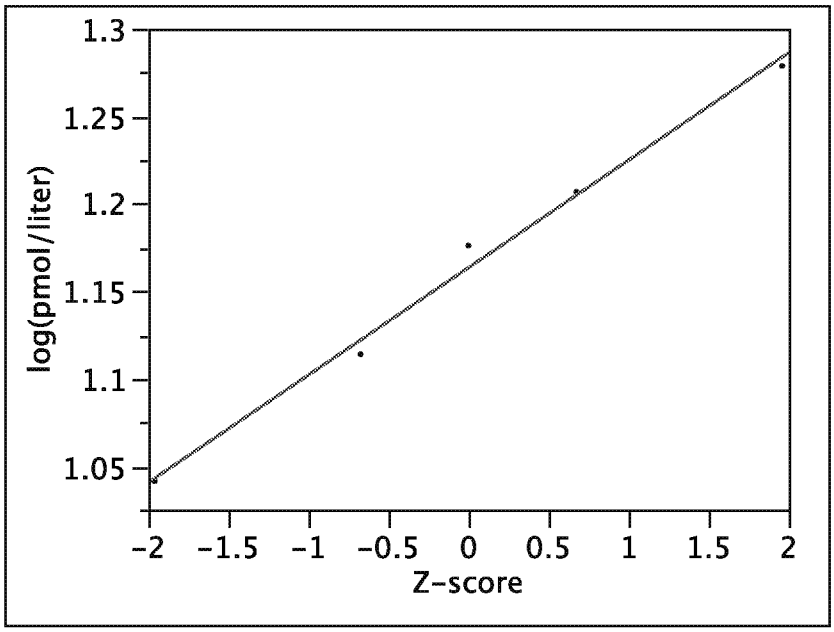
Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***
		Gong and Hoffman (2008) 1st trimester: **Lognormal Distribution Fit**



Linear Fit
log(pmol/liter) = 1.1634014 + 0.0614314*Z-score

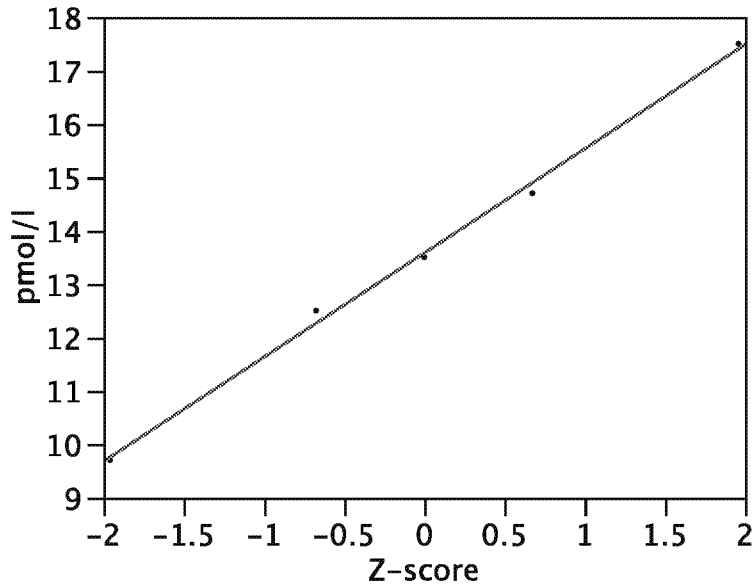
Summary of Fit

RSquare	0.992123
RSquare Adj	0.989498
Root Mean Square Error	0.009264
Mean of Response	1.163401
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.1634014	0.004143	280.82	<.0001
Z-score	0.0614314	0.00316	19.44	0.0003

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***
		Gong and Hoffman (2008) 2nd trimester **Normal Distribution Fit**



Linear Fit
pmol/l = 13.58 + 1.9518219*Z-score

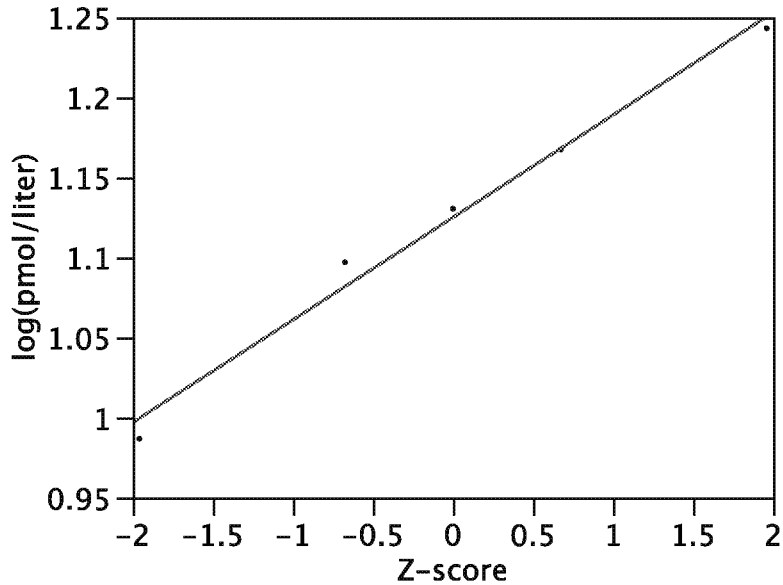
Summary of Fit

RSquare	0.996565
RSquare Adj	0.99542
Root Mean Square Error	0.193934
Mean of Response	13.58
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio
Intercept	13.58	0.08673	156.58
Z-score	1.9518219	0.066159	29.5

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***
		Gong and Hoffman (2008) 2nd trimester **Lognormal Distribution Fit**



Linear Fit
log(pmol/liter) = 1.1248742 + 0.0639794*Z-score

Summary of Fit

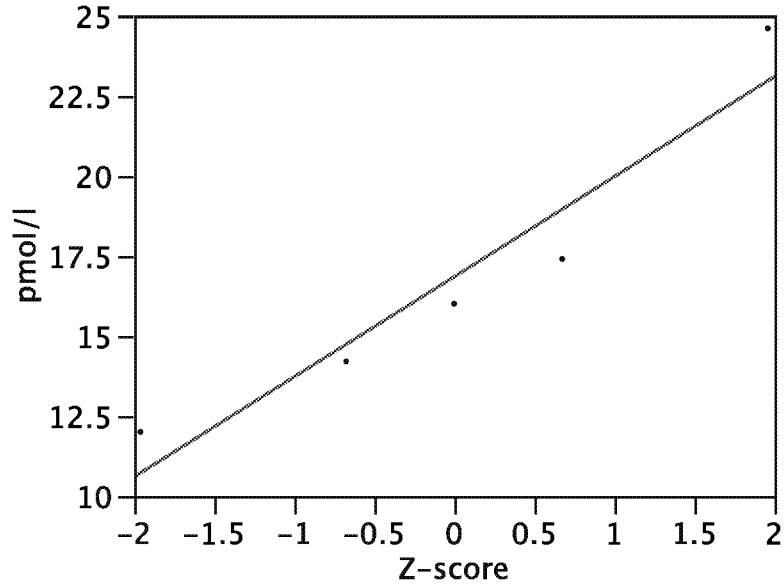
RSquare	0.986682
RSquare Adj	0.982242
Root Mean Square Error	0.01258
Mean of Response	1.124874
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio
Intercept	1.1248742	0.005626	199.94
Z-score	0.0639794	0.004292	14.91

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***

Wang et al. (2011) 1st trimester (random sample of women)
Normal Distribution Plot



Linear Fit
pmol/l = 16.84 + 3.1251679*Z-score

Summary of Fit

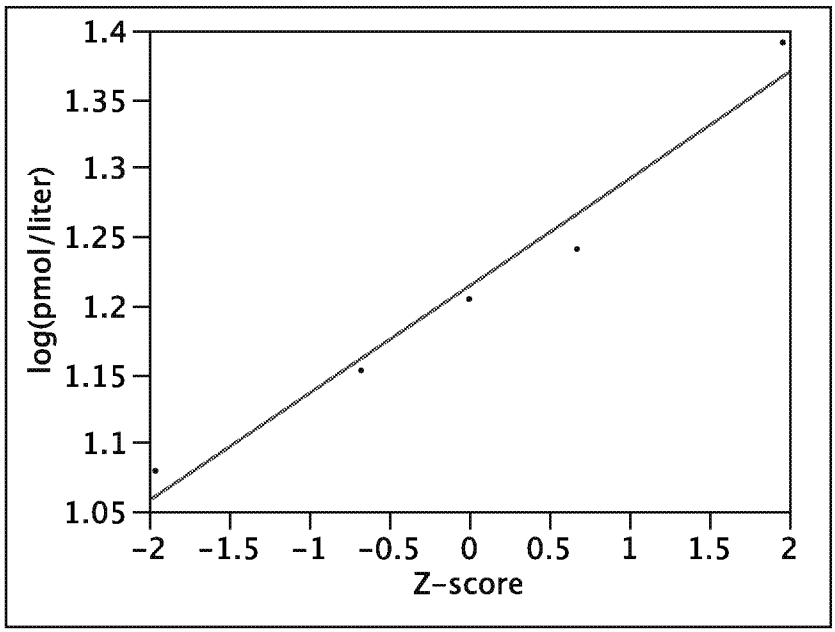
RSquare	0.91587
RSquare Adj	0.887827
Root Mean Square Error	1.603019
Mean of Response	16.84
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	16.84	0.716892	23.49	0.0002
Z-score	3.1251679	0.546854	5.71	0.0106

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***

Wang et al. (2011) 1st trimester (random sample of women)
Lognormal Distribution Plot



Linear Fit
log(pmol/liter) = 1.2134148 + 0.0780372*Z-score

Summary of Fit

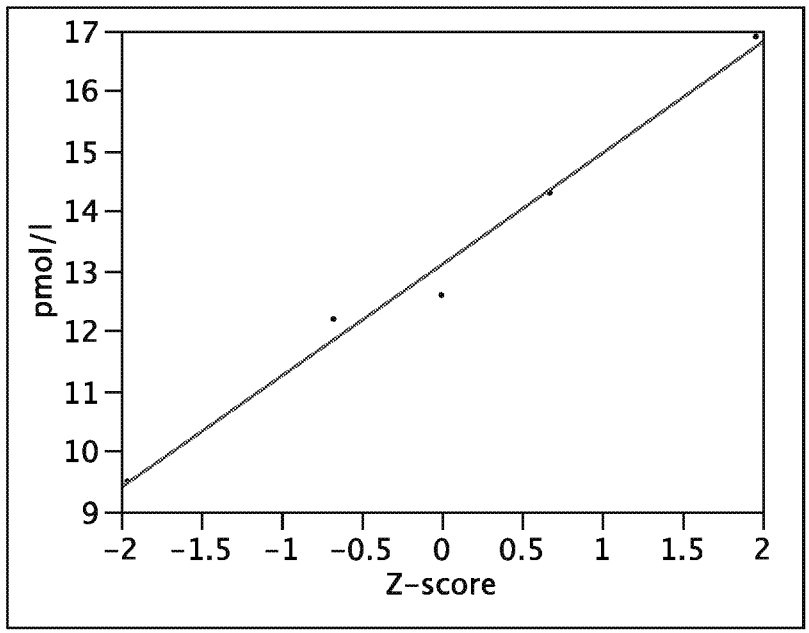
RSquare	0.967411
RSquare Adj	0.956548
Root Mean Square Error	0.02424
Mean of Response	1.213415
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.2134148	0.010841	111.93	<.0001
Z-score	0.0780372	0.008269	9.44	0.0025

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***

Wang et al. (2011) 2nd trimester (random sample of women)
Normal Distribution Plot



Linear Fit
pmol/l = 13.1 + 1.8527348*Z-score

Summary of Fit

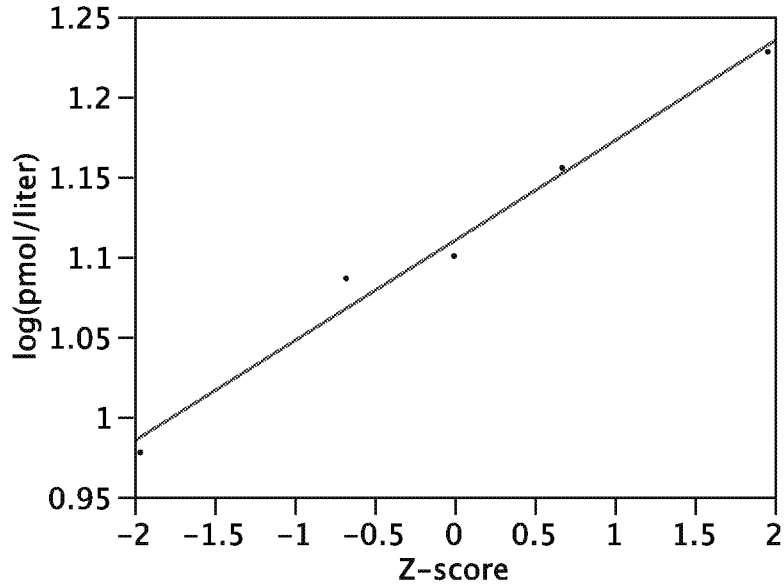
RSquare	0.986483
RSquare Adj	0.981977
Root Mean Square Error	0.367043
Mean of Response	13.1
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	13.1	0.164147	79.81	<.0001
Z-score	1.8527348	0.125213	14.8	0.0007

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***

Wang et al. (2011) 2nd trimester (random sample of women)
Lognormal Distribution Plot



Linear Fit
log(pmol/liter) = 1.1095353 + 0.062475*Z-score

Summary of Fit

RSquare	0.983535
RSquare Adj	0.978047
Root Mean Square Error	0.01368
Mean of Response	1.109535
Observations (or Sum Wgts)	5

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.1095353	0.006118	181.35	<.0001
Z-score	0.062475	0.004667	13.39	0.0009

Angela M. Leung, M.D., M.Sc.

No specific observations on Model Appendices provided.

Michael H. Lumpkin, Ph.D., DABT

No specific observations on Model Appendices provided.

Elizabeth N. Pearce, M.D., M.Sc.

Specific Observations on Model Appendices		
Page	***Line***	***Comment or Question***
App-17	7-10	"Also, the lactating mother has the demands of lactation, which clears iodide and T4 from her system. The mother's basal levels of fT4... are seen to decline 23% from postnatal day 7 to 90, which may be in part because the rate of milk ingestion, hence clearance of iodide and T4, is increasing": lactation does clear significant iodine from the system, but only a very trivial amount of thyroid hormone is secreted into breast milk, certainly not enough to contribute substantially to a decrease in maternal FT4.
App-17	21-22 and 30	It is noted in lines 21-22 that maternal fT4 stabilizes after 2-3 weeks postpartum (which makes sense, given that the half-life of TBG is about 5 days and that of T4 is about 8 days), but this seems to be partially contradicted by the statement in line 30 that maternal serum fT4 decreases with time. Line 30 refers to the right panel of Figure D-4, but I think it should be the right panel of figure C-1.
App-25	Table E-1	As noted above, it would be helpful to provide more information about study cohorts here, particularly with respect to exclusion of TPO and/or thyroglobulin antibody positive women and the population iodine status
App-34	9-10	With respect to pregnant women, "The amount of free iodide in the thyroid was assumed to be a very small quantity, negligible compared to the flux in and out": This is not consistent with the knowledge that the average adult thyroid in iodine-sufficient regions contains 10-20 mg of iodine (accounted for by the CTGIPOOL variables in the infants and lactating mothers).
App-36	18-22	It is noted that in infants if T4 production declines there will be a compensatory increase in the relative rate of T3 production. This is appropriate. However, it is stated that "This mechanism is not assumed to apply in the mother": It is unclear why this is not assumed in the mother, particularly because increases in the maternal ratio of T3:T4 in pregnancy produced could have deleterious effects on the fetus.

Stephen M. Roberts, Ph.D.

No specific observations on Model Appendices provided.

Joanne F. Rovet, Ph.D.

No specific observations on Model Appendices provided.

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VII. SPECIFIC OBSERVATIONS ON MODEL CODE

Hugh A. Barton, Ph.D.

No specific observations on Model Code provided.

Claude Emond, Ph.D.

Specific Observations on Model Code: 3352514 - Perchlorate-Iodide-Thyroid-Hormone BBDR Model for the Pregnant Mother and Fetus – acslX version	
File	***Comment or Question***
BBDRHPT_apr2015.csl	Line 26 Why a fix CONSTANT BW_f = 3.4 ! kg| Fetal BW at ~40th Gwk. Is it only the week 40th simulated?
	Line 79 is it the mass balance (MassB_Amount_i). Should not it be at 0?
BBDRPregModel2013.m	This file does not work. Error message

Specific Observations on Model Code: 3352515 - Perchlorate-Iodide-Thyroid-Hormone BBDR Model for the Lactating Mother and Infant – acslX version	
File	***Comment or Question***
ClO4 Fisher infant 2015	Line 428, 432, 435; why do you use variable clearance table function with time
	Line 518 and 526; the constant value are they refereed to Schlosser (2016)? If so add the reference.

Dale Hattis, Ph.D.

No specific observations on Model Code provided.

Angela M. Leung, M.D., M.Sc.

No specific observations on Model Code provided.

Michael H. Lumpkin, Ph.D., DABT

No specific observations on Model Code provided.

Elizabeth N. Pearce, M.D., M.Sc.

No specific observations on Model Code provided.

Stephen M. Roberts, Ph.D.

No specific observations on Model Code provided.

Joanne F. Rovet, Ph.D.

No specific observations on Model Code provided.

ED_005043_00057980-00110

Appendix A
List of Peer Reviewers and Biographical Sketches

External Peer Review Meeting for EPA's *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202-3526

January 10 and 11, 2017

LIST OF PEER REVIEWERS

Hugh A. Barton, Ph.D. (chair)
Pfizer, Inc.

Claude Emond, Ph.D.
University of Montreal

Dale Hattis, Ph.D.
George Perkins Marsh Institute, Clark University

Angela M. Leung, M.D., M.Sc.
UCLA David Geffen School of Medicine

Michael Lumpkin, Ph.D., DABT
Center for Toxicology and Environmental Health, LLC

Elizabeth N. Pearce, M.D., M.Sc.
Boston Medical Center/Boston University School of Medicine

Stephen M. Roberts, Ph.D.
University of Florida

Joanne F. Rovet, Ph.D.
Hospital for Sick Children (Toronto)

BIOGRAPHICAL SKETCHES OF PEER REVIEWERS

Hugh A. Barton, Ph.D.
Pfizer, Inc.

Dr. Barton is an Associate Research Fellow with Pfizer, Inc. in Groton, CT working on mechanistic modeling for pharmacokinetics and pharmacodynamics (PD). Previously he was a toxicologist with the US EPA developing computational models for use in biologically based dose-response analyses, particularly PBPK, for chemical risk assessment. He received his Ph.D. in Applied Biological Sciences from Massachusetts Institute of Technology in 1988. He specializes in the use of PBPK and mechanistic PD modeling to address low dose, interspecies, and inter-route extrapolations that critically impact estimating risks. He has evaluated volatile organic compounds, endocrine disrupting chemicals, and perfluorinated alkyl compounds, most recently focusing on comparisons across life stages. Dr. Barton has been an invited speaker at over 60 presentations, and has published nearly 200 publications, including peer-reviewed journal articles, technical documents, and abstracts. He served on the EPA Science Advisory Board (SAB) Perchlorate Advisory Panel. He has served as a reviewer for several journals including *Journal of Toxicology and Environmental Health, Reproductive Toxicology* and *Toxicology and Applied Pharmacology*. Dr. Barton is currently a member of and has been the

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President and Vice President of the Society of Toxicology (SOT) Risk Assessment Specialty Section and the SOT Biological Modeling Specialty Section and a member of the American Society of Pharmacometrics.

Claude Emond, Ph.D.
University of Montreal

Dr. Emond is an Adjunct Clinical Professor, Department of Environmental and Occupational Health, Faculty of Medicine, University of Montreal, Montréal, QC, Canada. He received his Ph.D. in Public Health with a concentration in toxicology from University of Montreal in 2001. His main research program is on toxicology and pharmacokinetic and pharmacodynamic modeling of toxic molecules with the objective to understand their mode of action for human health risk assessment. Dr. Emond has presented at 100 lectures, posters, and abstract presentations and has authored or co-authored of over 40 peer-reviewed scientific publications. He served on the EPA Science Advisory Board (SAB) Perchlorate Advisory Panel. In addition, Dr. Emond has been a consultant for US EPA, private company, and academic organizations in PBPK modeling.

Dale Hattis, Ph.D.
George Perkins Marsh Institute, Clark University

Dr. Hattis is a Research Professor with George Perkins Marsh Institute at Clark University. He received his Ph.D. in Genetics from Stanford University in 1974. He has been engaged in the development and application of quantitative methodologies to assess the health impacts of toxic chemicals. His work has focused on approaches to incorporate inter-individual variability data and quantitative mechanistic information into risk assessments for both cancer and non-cancer endpoints. His recent research has explored PBPK modeling of acrylamide dose in rats and humans, mechanism-based dose response modeling of carcinogenic effects from ionizing radiation, age-related differences in sensitivity to carcinogenesis and other effects, and ataxonomy of different non-mutagenic modes of action for carcinogenesis with likely differential implications for age-related sensitivity. Dr. Hattis has authored or co-authored nearly 250 publications and is the primary author of the article entitled "Tests of Three Effect-Addition Hypotheses for the Combined Action of Iodide Dietary Deficiency and Perchlorate on Thyroid Hormone Levels" (2004). In addition, he has evaluated the USEPA/OSWER Preliminary Remediation Goal for perchlorate in groundwater with a focus on exposure to nursing infants. He is a member of the Environmental Health Committee of the EPA Science Advisory Board and was the past Chair of the Dose Response Specialty Group of the Society for Risk Analysis. Has been a member of several National Research Council committees addressing human health risk assessment topics.

Angela M. Leung, M.D., M.Sc.
UCLA David Geffen School of Medicine

Dr. Leung is a Clinical Assistant Professor of Medicine at University of California Los Angeles, David Geffen School of Medicine. Dr. Leung is the Director of the West Los Angeles VA Medical Center thyroid/lipid clinic. Her research focus is in iodine nutrition, thyroid disease, epidemiology, and women's health. She has studied the effects of environmental inhibitors

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(primarily perchlorate and thiocyanate) on iodine availability and thyroid function in mothers and their infants, the iodine content of U.S. prenatal multivitamins, and factors affecting breastmilk iodine concentrations. She maintains interests in clinical research studies related to iodine status and thyroid function, particularly during pregnancy and lactation. Dr. Leung was the Principal Investigator on a research project examining the relationships between iodine sufficiency of lactating women and their infants, environmental perchlorate and cigarette smoke exposure, and infant thyroid function. Dr. Leung has been an invited speaker at nearly 50 national and international meetings/workshops, and has authored or co-authored over 100 publications, including peer-reviewed journal articles, reviews and book chapters, editorials, case reports, media interviews, abstracts, and poster abstract presentations on topics related to iodine and the thyroid. Dr. Leung served on the editorial board of the *Journal of Clinical and Translational Endocrinology* and *Thyroid* and is an associate editor for *Clinical Thyroidology* and *BMC Endocrine Disorders*. Dr. Leung serves as an ad hoc reviewer for journals such as *Thyroid Endocrinology* (of *Frontiers in Endocrinology*) and *Clinical Endocrinology*. She is a member of the American Association of Clinical Endocrinology, Endocrine Society, and American Thyroid Association.

Michael H. Lumpkin, Ph.D., DABT
Center for Toxicology and Environmental Health, LLC

Dr. Lumpkin is a board-certified consulting toxicologist at the Center for Toxicology and Environmental Health, LLC, practicing in chemical dose-response assessment, PBPK modeling, dose reconstruction, product safety assessments, and chemical emergency response. He received his Ph.D. in Toxicology from University of Georgia in 2002. Dr. Lumpkin has developed, critiqued, and applied PBPK models for risk assessment of drinking water disinfection by-products in pregnant animals and fetuses, VOCs, metals, pesticides and bioterrorism agents for USEPA, CDC and DOD, for use in regulatory standard support and emergency planning. He presented an analysis of critical endpoints for perchlorate drinking water standard derivation at the 2012 Society of Toxicology (SOT) annual meeting, and provided public comments based on this analysis to the EPA SAB Stakeholders' meeting that same year. He was a co-author of a published study on the pharmacokinetics of perchlorate and its effects on the hypothalamus/pituitary-thyroid axis. He presented PBPK model data and analysis for various compounds at the 2008, 2009, 2013, and 2014 SOT annual meetings. Dr. Lumpkin has coauthored numerous peer-reviewed hazard assessments for USEPA and the Agency for Toxic Substances and Disease Registry (ATSDR). He served as Councilor, Vice President, and President of the Southeastern Regional Chapter of the SOT from 2010-2013. He served as Councilor of the Risk Assessment Specialty Section of the SOT from 2014-2016. He has also served as a peer reviewer for toxicology journals, and has lectured in graduate risk assessment courses. He has been a member of the SOT since 1998 and is certified as a Diplomate of the American Board of Toxicology.

ED_005043_00057980-00114

Elizabeth N. Pearce, M.D., M.Sc.
Boston Medical Center/Boston University School of Medicine

Dr. Pearce is an Associate Professor of Medicine at Boston Medical Center/Boston University School of Medicine. She received her M.D. from Harvard School of Medicine in 1997 and her M.Sc. in Epidemiology from Boston University School of Public Health in 2004. She conducts clinical and epidemiologic research in areas including the sufficiency of dietary iodine, thyroid function in pregnancy, the thyroid effects of environmental perchlorate exposure and other potential endocrine disruptors, and the cardiovascular effects of subclinical thyroid dysfunction. Dr. Pearce is currently involved in a project supported by NIH/NIEHS investigating the relationships between perchlorate, iodine, and thiocyanate and thyroid function in a cohort of pregnant women and their infants. Dr. Pearce has been an invited speaker at nearly 100 national and international meetings/workshops, and has authored or co-authored nearly 200 publications/abstracts. In addition, Dr. Pearce has served on the editorial boards of several journals including *Endocrine Practice*, *Thyroid,* and *Thyroid Research* and is an associate editor for *Clinical Thyroidology* and *Thyroid*. She is a member of and has served on the board of directors for the American Thyroid Association and is an active member of the Endocrine Society.

Stephen M. Roberts, Ph.D.
University of Florida

Dr. Roberts is the Director of the Center of Environmental and Human Toxicology at the University of Florida. He received his Ph.D. in Pharmacology (1977) from University of Utah, Salt Lake City, UT. His current research interests include mechanisms of drug and chemical toxicity; cell defense mechanisms against toxicity; toxicokinetics, particularly bioavailability of environmental contaminants; risk assessment; nanomaterial toxicity; and novel gene therapy approaches for cancer. Dr. Roberts served as chair on the EPA Science Advisory Board (SAB) Perchlorate Advisory Panel and co-authored the *SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate*. He is the Associate Editor and serves on the editorial advisory board of *Nanotoxicology* and has served on the editorial advisory board of *Toxicology and Applied Toxicology, Human and Ecological Risk Assessment*, and *Dose-Response*. He has authored or co-authored over 100 manuscripts, over 100 abstracts or letters and 19 book chapters, and has edited four textbooks: *Hazardous Waste Incineration: Evaluating the Human Health and Environmental Risks*; *Principles of Toxicology: Environmental and Industrial Applications* (1st and 3rd editions); and *Oxidative Stress in Applied & Basic Research and Clinical Practice. Studies on Experimental Toxicology and Pharmacology*. Dr. Roberts is a member of the Society of Toxicology, Society for Risk Analysis, and American Society for Pharmacology and Experimental Therapeutics.

Joanne F. Rovet, Ph.D.
The Hospital for Sick Children (Toronto)

Dr. Rovet is a Senior Scientist in Neurosciences & Mental Health Program at The Hospital for Sick Children and a professor of Pediatrics, Psychology, and Institute of Medical Sciences at the University of Toronto. She received her Ph.D. from the University of Toronto in 1983. She has conducted clinical research and her research interests include the role of thyroid hormone in fetal

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and neonatal brain development, structural and functional neuroimaging studies of children with fetal/neonatal thyroid hormone insufficiencies, thyroid hormone and visual development, and hypothyroxinemia of prematurity and child outcome. A primary focus of Rovet's research program is studying children who were exposed to insufficient levels of thyroid hormone during fetal life and early infant development. Dr. Rovet has consulted to the NIEHS, NIAAA, Environmental Defense League, Health Canada, and the US EPA, having been a member of the EPA Scientific Advisory Board (SAB) Perchlorate Advisory Panel member. Dr. Rover has been an invited speaker at over 50 workshops, and has authored or co-authored over 150 publications, including peer-reviewed journal articles, technical reports, books, abstracts, and poster abstract presentations. In addition, Dr. Rovet is an editor for *Frontiers in Endocrinology, Thyroid Endocrinology* and *Thyroid Research* and has served on the editorial board of *Thyroid.* She is an elected member of the American Thyroid Association and a member of the Endocrine Society.

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Appendix B
Meeting Agenda

AGENDA

External Peer Review Meeting for EPA's *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*

January 10, 2017 8:30 AM to 5 PM (EST),
January 11, 2017 8:30 AM to 2 PM (EST)

Day 1	Teleconference number (415) 655-0060	Code: 799-089-154
Day 2	Teleconference number (562) 247-8321	Code: 973-657-785

Day 1 Webinar Link: https://attendee.gotowebinar.com/register/6386457593790855172
Day 2 Webinar Link: https://attendee.gotowebinar.com/register/8791712946830139140

DAY 1 – January 10, 2017

8:30 AM EST **Meeting Registration & Sign-in**

9:00 AM EST **Welcome, Goals of Meeting, and Introductions**
Karie Riley, Versar, Inc.

9:15 AM EST **EPA's Introduction to the Meeting**
Eric Burneson, U.S. EPA,
Director, Standards and Risk Management Division

9:25 AM EST **Chair's Introduction to the Meeting**
Hugh Barton, Chair

9:30 AM EST **Biologically Based Dose-Response Models Predicting Serum Thyroid Hormones (THs): Background on Development / Q&A for Panel**
Jeff Fisher, U.S. FDA

10:00 AM EST **Iodine/Perchlorate BBDR Model: Context, Overview of Results, and Focus / Q&A for Panel**
Paul Schlosser, U.S. EPA

10:30 AM EST *Break**

10:45 AM EST **Observer Comment Session**

11:00 AM EST **Chair's Review of Charge**
Hugh Barton, Chair

11:05 AM EST **Discussion – Round Table General Overview Comments**

11:30 PM EST *Lunch**

12:30 PM EST **Discussion - Response to Charge Questions (Initial Question(s))**

**Time for breaks and lunch are approximate and at the Chair's discretion.*

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AGENDA

External Peer Review Meeting for EPA's *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*

January 10, 2017 8:30 AM to 5 PM (EST),
January 11, 2017 8:30 AM to 2 PM (EST)

Day 1	Teleconference number (415) 655-0060	Code: 799-089-154
Day 2	Teleconference number (562) 247-8321	Code: 973-657-785

Day 1 Webinar Link: https://attendee.gotowebinar.com/register/6386457593790855172
Day 2 Webinar Link: https://attendee.gotowebinar.com/register/8791712946830139140

DAY 1 – January 10, 2017 (continued)

2:30 PM EST *Break**

2:45 PM EST **Discussion - Response to Charge Questions (continued)**

4:45 PM EST **Wrap-up**

5:00 PM EST Adjourn

DAY 2 – January 11, 2017

8:30 AM EST **Recap of Day 1 and Agenda for Day 2**
Karie Riley, Versar, Inc.

8:35 AM EST **Introduction to Meeting for Day 2**
Peter Grevatt, U.S. EPA
Director, Office of Ground Water and Drinking Water

8:45 AM EST **Chair's Review of Charge for Day 2**
Hugh Barton, Chair

8:50 AM EST **Discussion – Response to Charge Questions (continued)**

10:00 AM EST *Break**

10:15 AM EST **Discussion – Response to Charge Questions (continued)**

11:30 PM EST *Lunch**

12:30 PM EST **Discussion – Response to Charge Questions (continued)**

1:50 PM EST **Wrap-up/Next Steps**
Karie Riley, Versar, Inc.

2:00 PM EST Adjourn

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Appendix C
List of Observers

External Peer Review Meeting for EPA's *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202

January 10 and 11, 2017

LIST OF REGISTERED OBSERVERS

Eileen Abt (on phone)
U.S. FDA/CFSAN

Erica Bernstein
The Chlorine Institute

Scott Biernat
Association of Metropolitan Water Agencies (AMWA)

Thomas D. Blackman
Lockheed Martin Corporation

Lauren Brown
Abt Associates

Eric Burneson
U.S. EPA

Gail Charnley
HealthRisk Strategies LLC

Lisa Christ
U.S. EPA

Lisa Corey
Intertox

William S. Eck (on phone)
U.S. Army Public Health Center

Jeff Fisher
U.S. FDA

Lynn Flowers
U.S. EPA

Jessica Georges
U.S. EPA

Mark Gibson
American Chemistry Council

Jonathan Gledhill
Policy Navigation Group

Peter Grevatt
U.S. EPA

Ahmed Hafez
U.S. EPA

Erik Helm
U.S. EPA

Sam Hernandez
U.S. EPA

John Herrmann (on phone)
Policy Navigation Group

Caryn Kelly (on phone)
Amec Foster Wheeler

Jonathan Koplos (on phone)
The Cadmus Group, Inc.

Jason Leuck
Lockheed Martin Corporation

Thomas Lewandowski (on phone)
Gradient Corporation

Bruce Maclear (on phone)
U.S. EPA Region 9

Greg Miller
U.S. EPA

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External Peer Review Meeting for EPA's *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*

Crystal City Marriott at Reagan National Airport
1999 Jefferson Davis Highway
Arlington, VA, 22202

January 10 and 11, 2017

LIST OF REGISTERED OBSERVERS (continued)

Kevin M. Morley (comments)
American Water Works Association

Mary P. Morningstar
Lockheed Martin Corporation

Daniel Olson
U.S. EPA

Sandra O'Neill
U.S. EPA

Darrell Osterhoudt
Association of State Drinking Water Administrators

Russ Perkinson
U.S. EPA

Richard Pleus (comments)
Intertox

Jim Rollins
Policy Navigation Group

Paul Schlosser
U.S. EPA

David Schultz
Bloomberg BNA

Steve Shost
NYS Department of Health

Ed Thomas
The Fertilizer Institute

Clifton Townsend
U.S. EPA

Shradha Upadhayay (on phone)
Metropolitan Water District of Southern California

Linda S. Wennerberg
NASA

Linda M. Wilson (on phone)
NYS Office of the Attorney General

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Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 10/20/2016 7:41:03 PM
To: Oshida, Phil [Oshida.Phil@epa.gov]; Ohanian, Edward [Ohanian.Edward@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Perchlorate BBDR Model Peer Review Selection Report
Attachments: TO 2015-22 Draft Reviewer Selection Report to EPA 10.19.16.pdf; Appendix D Biosketches 10.19.16.pdf; Appendix C Reviewer Information 10.19.16.pdf; Appendix B COI Certification Letter 10.19.16.pdf

FYI – attached materials are for the 10/27 meeting. I'll be setting up a pre-meeting early next week.

From: Perkinson, Russ
Sent: Thursday, October 20, 2016 8:25 AM
To: O'Farrell, Thomas <OFarrell.Thomas@epa.gov>
Cc: Greene, Mary <greene.mary@epa.gov>; Grifo, Francesca <Grifo.Francesca@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>
Subject: Perchlorate BBDR Model Peer Review Selection Report

Tom – I've reviewed this selection report prepared by the contractor for the perchlorate BBDR model peer review and find it acceptable for distribution to the meeting attendees. Be advised that the comment period on the list of interim peer reviewers runs through October 21. Since you need the materials now (in advance of the comment close date) to provide adequate time for review, I instructed the contractor to place a "draft" mark on the document. If there are comments received before the end of the comment period, it is possible that some modifications will be needed. We will make you aware of any changes, if needed, early next week.

From your email yesterday, I'm assuming you or others in your office will attach the documents to the calendar entry for the meeting or otherwise will distribute to the total list of meeting attendees. If you want me to send it to the whole list, Please let me know. I'm just copying Mary and Francesca per your instructions along with my branch chief and the perchlorate team lead. **Since you indicate you are in a meeting today, I'd appreciate it if Mary or Francesca reply to me this morning if I am to distribute it to all attendees.**

Since an exact date has not been selected for the panel meeting and due to the range in expertise we are seeking, I asked the contractor to provide eight names for the final panel along with several alternates having varied expertise (primarily in the event that the precise date selected conflicts with a reviewer's availability).

Regards,
Russ

Russ Perkinson
U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
1200 Pennsylvania Ave., NW
Mail Code 4607M
Washington, DC 20460
perkinson.russ@epa.gov
Phone: (202) 564-4901

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 6/1/2020 6:29:08 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
Subject: FW: FOR REVIEW: draft perchlorate response to comment document
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-19-20 v2.docx

Hi Sam,
Can you please focus on addressing any comments in chapters 1-7?
Thanks
lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, June 01, 2020 2:24 PM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: FW: FOR REVIEW: draft perchlorate response to comment document

Crystal and Lisa;
Jennifer spoke with me today about her comments on the perchlorate response to comment document. She has reviewed the Chapters 1-7 and is in the midst of reviewing Chapter 8. She stated that the responses in Chapters 1-7 are well written.
She is concerned that Chapter 8 contains some redundant responses in which the same issues are addressed. She asked that someone review chapter 8 responses with an eye toward reducing redundant responses and assuring that we don't have inconsistent language contained where we do have redundant responses. Crystal since you were able to do that effectively for Lead Free, I would like your help in doing that in Chapter 8 of the attached document.

Please note that

1. Jennifer is continuing with her review and will forward the document to Charlotte B with the understanding we can make combine changes that Crystal makes with any changes that result from Jennifer and Charlotte's review.
2. Jennifer prefers the Lead Free approach to summary responses for each section. She does not want us to change what we have done for perchlorate but when we prepare the LCR response to comment document she wants it to look more like the Lead Free document than the perchlorate document.

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, May 19, 2020 6:41 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FOR REVIEW: draft perchlorate response to comment document

DRAFT/DELIBERATIVE
Hello Jennifer,
Attached for your is the draft perchlorate response to comment document. Please let us know if you have questions or concerns.
Thanks,
Lisa

Message

From: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Sent: 5/20/2020 11:38:25 AM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]
Subject: Important: Perchlorate submittal to OW
Attachments: Perchlorate Action Memo 5-19-20.docx; Draft Perchlorate Final Action FRN 5-19-20 v1.docx; Final Perchlorate Action for 12866 Review Transmittal Memo OGWDW to OW 5-19-20.pdf; 12866docketguidelines-09-27-10.pdf

Importance: High

Good Morning,

There's some confusion in OW over our submittal of the perchlorate docs. for Charlotte's review. Joe asked that I enter the attached documents into CMS (w/o review) for Charlotte. Is this the formal submittal? To initiate OMB Review, we need to follow the Action Development Process checklist (as applicable) and label the FRN per the attached guidance. (Note: submit the FAR memo and associated concurrences in on PDF file.)

Thanks for your timely attention…any questions, please let me know, thanks!

OMB REVIEW OF RULE

Left Side	***Right Side***
□ OGC Concurrence e-mail (or letter) □ Core Workgroup concurrences: emails: ORD, OPEI , OECA □ FAR memo and attached Workgroup FAR concurrences □ Draft Economic Analysis (1 + e copy) * □ Note: Docket Guidelines https://intranet.epa.gov/actiondp/documents/12866docketguidelines-09-27-10.pdf	□ Transmittal Memo from DD to OD □ Transmittal Memo from OD to AA (Orig + yellow) □ Transmittal Memo from AA to OPEI (Orig + yellow) □ Draft Action Memo from AA to Administrator □ Draft Rule and Preamble FRN □Send all Files electronically to IO (SF) – will forward to OP https://intranet.epa.gov/actiondp/adp-templates/index.htm#adp

6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141 and 142

[EPA-HQ-OW-2018-0780, EPA–HQ–OW–2008–0692, EPA–HQ–OW– 2009–0297; FRL-XXXX-XX-OW]

RIN 2040-AF28

Drinking Water: Notice of Final Action on Perchlorate

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final Action.

SUMMARY: The Environmental Protection Agency (EPA) is announcing its withdrawal of the 2011 determination to regulate perchlorate in accordance with the Safe Drinking Water Act (SDWA). On February 11, 2011, the EPA published a *Federal Register* notice in which the Agency determined that perchlorate met the SDWA's criteria for regulating a contaminant. On June 26, 2019, the EPA published a proposed national primary drinking water regulation (NPDWR) for perchlorate and requested public comments on multiple alternative regulatory actions, including the alternative of withdrawing the 2011 regulatory determination for perchlorate. The EPA received approximately 1,500 comments on the proposed rule. The EPA has considered these public comments and based on the best available information the Agency is withdrawing the 2011 regulatory determination and is making a final determination to not regulate perchlorate. The EPA has determined that perchlorate does not occur with a frequency

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and at levels of public health concern, and that regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems.

DATES: For purposes of judicial review, the regulatory determination in this document is issued as of *[insert date of publication in the* Federal Register*]*.

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This notice is organized as follows:

I. General Information

A. Does this Action Apply to Me?

B. How can I get Copies of this Document and other Related Information?

II. Background

A. What is Perchlorate?

B. What is the Purpose of this Action?

C. What is the EPA's statutory authority for this action?

D. Statutory Framework and Perchlorate Regulatory History

III. Final Regulatory Determination for Perchlorate

A. May perchlorate have an adverse effect on the health of persons?

B. Is perchlorate known to occur or is there a substantial likelihood that perchlorate will occur in public water systems with a frequency and at levels of public health concern?

C. Is there a meaningful opportunity for the reduction of health risks from perchlorate for persons served by public water systems?

D. What is the EPA's final regulatory determination on perchlorate?

IV. Summary of Key Public Comments on Perchlorate

A. Health Effects Assessment

B. Occurrence

C. Regulatory Proposal and Alternatives

D. SDWA Statutory Requirements

E. Regulatory Determination Withdrawal

V. Conclusion

VI. References

I. General Information

A. Does This Action Apply to Me?

This action will not impose any requirements on anyone. Instead, this action notifies interested parties of the EPA's withdrawal of the 2011 regulatory determination for perchlorate and the final regulatory determination to not regulate perchlorate. This notice also provides a summary of the major comments received on the June 26, 2019 (84 FR 30524) proposed NPDWR for perchlorate.

B. How can I get Copies of this Document and other Related Information?

The EPA has established a docket for this action under Docket ID No. EPA–HQ–OW–2018–0780. Publicly available docket materials are available electronically at [HYPERLINK "http://www.regulations.gov/docket?D=EPA-HQ-OW-2018-0780"].

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. Perchlorate can also result from the degradation of hypochlorite solutions used for water disinfection. The degradation into perchlorate occurs when hypochlorite solutions are improperly stored and handled. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water. At certain levels, perchlorate can prevent the thyroid gland from getting enough iodine, which can affect thyroid hormone production. For pregnant women with low iodine levels, sufficient changes in thyroid

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hormone levels may cause changes in the child's brain development. For infants, changes to thyroid hormone function can also impact brain development.

B. What is the purpose of this action?

The purpose of this action is to publish the EPA's notice to withdraw the 2011 regulatory determination and issue a final determination to not regulate perchlorate in drinking water. This notice presents the EPA's basis for this withdrawal and final regulatory determination, and the EPA's response to key issues raised by commenters in response to the June 26, 2019 (84 FR 30524) proposed rule (referred to hereinafter as "the 2019 proposal").

C. What is the EPA's statutory authority for this action?

The SDWA sets forth three criteria that must be met for the EPA to issue a maximum contaminant level goal (MCLG) and promulgate a national primary drinking water regulation (NPDWR). Specifically, the Administrator must determine that (1) "the contaminant may have an adverse effect on the health of persons"; (2) "the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern"; and (3) "in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems" (SDWA 1412(b)(1)(A)).

The EPA has determined, based on data and analysis since the issuance of the 2011 regulatory determination, that perchlorate does not in fact meet the statutorily-prescribed criteria for regulation. As described in Sections III & VI of the 2019 proposal, the data and analysis in

the record indicate that perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Specifically, the peer-reviewed health effects analysis indicates that the concentration of perchlorate representing the proposed MCLG alternatives for levels of public health concern (18-90 µg/L) is higher than the concentration considered in issuance of the 2011 regulatory determination (1-47 µg/L) (USEPA, 2019a). In addition, based on an evaluation of the nationally representative UCMR 1 systems, the updated occurrence analysis shows that the frequency of occurrence of perchlorate in public water systems at levels exceeding any of the alternative proposed MCLGs is significantly lower (0.38% - 0.02%) than the frequency considered in the analysis for the 2011 regulatory determination (4% - 0.39%) (USEPA, 2019b). The EPA estimates that, even at the most stringent regulatory level considered in the 2019 proposal (18 µg/L), not more than 15 systems (0.03% of all water systems in the U.S.) would need to take action to reduce levels of perchlorate. Based on this information, the EPA determines that perchlorate does not occur in public water systems "with a frequency…of public health concern" and thus does not meet the second criterion of the three required for regulation under the SDWA. In addition, while the third criterion is "in the sole judgement of the Administrator," the low occurrence provides ample support for the EPA's conclusion that the regulation of perchlorate does not present a "meaningful opportunity for health risk reduction for persons served by public water systems," within the meaning of 1412(b)(1)(A)(iii). Accordingly, because perchlorate no longer meets the statutory criteria for regulation, the EPA does not have the authority to issue a MCLG or promulgate a NPDWR for perchlorate.

The EPA's decision to withdraw the regulatory determination is supported by the legislative history underlying the 1996 amendments to the SDWA, which repealed the statutory requirement for the EPA to regulate an additional 25 contaminants every 3 years and replaced it with the current requirement for the EPA to determine whether regulation is warranted for five contaminants every five years. In describing the need for such amendment, the legislative history points to the view expressed at the Committee Hearing that "the current law is a one-size-fits-all program. It forces our water quality experts to spend scarce resources searching for dangers that often do not exist rather than identifying and removing real health risks from our drinking water" (S. Rep. 104-169 (1995) at 12). This amendment reflected Congress' clear intent that the EPA prioritize actual health risks in determining whether to regulate any particular contaminant. *See id* at 12 (noting that the amendment "repeals the requirement that the EPA regulate an additional 25 contaminants every 3 years replacing it with a new selection process that gives the EPA the discretion to identify contaminants that warrant regulation in the future").

The EPA's decision to withdraw the regulatory determination is also consistent with Congress' direction to prioritize the SDWA decisions based on the best available public health information. *See* 1412(b)(1)(B)(ii)(II) (findings supporting a determination to regulate "shall be based on the best available public health information"); 1412(b)(2)(A) (requiring that the EPA use "the best available, peer-reviewed science and supporting studies…" in carrying out any actions under this section). Although the EPA determined in 2011 that perchlorate met the criteria for regulation, new data and analysis developed by the Agency as part of the 2019

proposal demonstrate that the occurrence and health effects information used as the basis for the 2011 determination no longer constitute "best available information," are no longer accurate and no longer support the Agency's prioritization of perchlorate for regulation. Accordingly, not only is EPA not authorized to issue a MCLG or promulgate a NPDWR for perchlorate, but it would not be in the public interest to do so.

The EPA recognizes that the Act does not include a provision explicitly authorizing withdrawal of a regulatory determination. However, such authority is inherent in the authority to issue a regulatory determination under 1412(b)(1)(B)(ii)(II), particularly given the requirement that such determination be based on the "best available public health information," as discussed above. Accordingly, the EPA must have the inherent authority to withdraw a regulatory determination if the underlying information changes between regulatory determination and promulgation. In light of its concern that the EPA focus new contaminant regulations on priority health concerns, Congress could not have intended that the EPA's regulatory decision-making be hamstrung by older data when newer, more accurate scientific and public health data are available, especially when those data demonstrate that regulation of a new contaminant would not present a meaningful opportunity for health risk reduction.

Moreover, the EPA notes that the statute specifically provides that a decision to <u>not</u> regulate a contaminant is a final Agency action subject to judicial review. The SDWA, section 1412(b)(1)(B)(ii)(IV). Congress could have – but did not – specify the same with respect to determinations <u>to</u> regulate. Congress also did not explicitly prohibit the EPA from withdrawing

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or modifying a regulatory determination. Congress' silence with respect to determinations to regulate suggests that Congress intended that such a determination is not itself a final agency action, but rather, a preliminary step in a decision-making process culminating in a NPDWR and thus, subject to reconsideration based on new data and analysis considered during the 36 month promulgation process specified in the statute. Accordingly, reconsideration of this preliminary finding – and withdrawal of the determination based on subsequent analysis mandated for NPDWR development – is fully consistent with the statutory decision-making framework.

D. Statutory Framework and Perchlorate Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to federal drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998 (63 FR 10274), 2005 (70 FR 9071), and 2009 (74 FR 51850).

The EPA collects data on the CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in public water systems. The SDWA, section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after consideration of public comment, issue a determination of whether or not to regulate at least five contaminants on each CCL. For any contaminant that the EPA determines meets the SDWA criteria for

regulation, under the SDWA, section 1412(b)(1)(E), the EPA must propose a NPDWR within two years and promulgate a final regulation within 18 months of the proposal (which may be extended by 9 additional months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water systems. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems and non-transient, non-community water systems. The first four UCMRs collected data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556), which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999). Water system monitoring data for perchlorate was collected from 2001 to 2005.

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. In its 2005 report, the NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule

[1] For the purposes of this notice, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

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known as the sodium/iodide symporter (NIS), which may lead to decreases in two thyroid hormones, thyroxine (T3) and triiodothyronine (T4), and increases in thyroid-stimulating hormone (TSH) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the NRC's recommended RfD of 0.7 µg/kg/day for perchlorate. The reference dose is an estimate of a human's daily exposure to perchlorate that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/

6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination to not regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA found that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 µg/L based on the RfD of 0.7 µg/kg/day and body weight and exposure information for pregnant women in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA, 2008a)","plainCitation":"(USEPA, 2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate

List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Using the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the EPA found that perchlorate did not occur at a frequency and at levels of public health concern. The EPA also determined there was not a meaningful opportunity for a NPDWR for perchlorate to reduce health risks.

In August 2009, the EPA published a supplemental request for comment with new analysis that derived potential alternative Health Reference Levels (HRLs) for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information, resulting in comparable perchlorate concentrations in drinking water, based on life stage, of between 1 μg/l to 47 μg/l (74 FR 41883; USEPA, 2009).

In February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011) after careful consideration of public comments on the October 2008 and August 2009 notices. The EPA found at that time that perchlorate may have an adverse effect on the health of persons, it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA stated then that: "*Based on the data in Table 1 and the range of potential alternative HRLs, EPA has determined that perchlorate is known to occur or there is a substantial likelihood that it will occur with a frequency and at levels of public health concern.*"(USEPA, 2011, p. 7765). The EPA found that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally estimated in the 2008 notice.

As a result of the determination, and as required by the SDWA, section 1412(b)(1)(E), the EPA initiated the process to develop a MCLG and a NPDWR for perchlorate.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory

determination. In the request, the Chamber claimed that the UCMR 1 data used in the EPA's occurrence analysis did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data in the analysis for systems in California and Massachusetts, using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

As required by section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. In May 2013, the SAB recommended that the EPA:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;

- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition—to thyroid hormone changes—and finally to neurodevelopmental impacts; and
- ''Extend the [BBDR] model expeditiously to . . . provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages''(SAB for the U.S. EPA, 2013, p. 19).

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, *i.e.,* breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). The EPA considered the recommendations from the 2017 peer review and made necessary model revisions to increase the scientific rigor of the model and the modeling results.

The EPA convened a second independent peer review panel in January 2018 to evaluate the revisions to the BBDR model. The EPA also presented several approaches to link the thyroid

hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018).

In response to a lawsuit brought to enforce the deadlines in the SDWA, section 1412(b)(1)(E), on October 18, 2016, the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to sign for publication a proposal for a MCLG and NPDWR for perchlorate in drinking water no later than October 31, 2018, and to sign for publication a final MCLG and NPDWR for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose a MCLG and NPDWR for perchlorate in drinking water was later extended to May 28, 2019, and the date for signature of a final MCLG and NPDWR was extended to be no later than June 19, 2020. The consent decree is available in the docket for this action.

In compliance with the deadline established in the consent decree, on May 23, 2019, the EPA Administrator signed a proposed rulemaking notice seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. The proposed rulemaking notice was published in the *Federal Register* on June 26, 2019. 84 Fed. Reg. 30524. The EPA proposed a NPDWR for perchlorate with an MCL and MCLG of 56 µg/L. The proposed MCLG of 56 µg/L was based on avoiding a 2 point IQ decrement associated with exposure to perchlorate in drinking water during the most sensitive life stage (the fetus) within a specific segment of the population (iodine deficient pregnant women).

The EPA also requested comment on two alternative MCL/MCLG values of 18 µg/L and 90 µg/L. These alternatives were based upon avoiding 1 point and 3 point IQ decrements respectively, associated with perchlorate exposure. Additionally, the EPA requested comment on whether the 2011 regulatory determination should be withdrawn, based on new information including updated occurrence data on perchlorate in drinking water and new analysis of the concentration of perchlorate in drinking water that represents a level of health concern.

III. Withdrawal of the 2011 Regulatory Determination and Final Determination to Not Regulate Perchlorate

In determining whether to regulate a particular contaminant, the EPA must follow the criteria mandated by the 1996 SDWA Amendments. Specifically, in order to issue a MCLG and NPDWR for perchlorate, the EPA must determine that perchlorate "may have an adverse effect on the health of persons," that perchlorate occurs at "a frequency and at levels of public health concern" in public water systems, and that regulation of perchlorate in drinking water systems "presents a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA, section 1412(b)(1)(A). In preparing the 2019 proposal for perchlorate, the EPA updated and improved information on the levels of public health concern and the frequency and levels of perchlorate in public water systems. The following is the EPA's reassessment of the regulatory determination criteria applied to the best available health science and occurrence data for perchlorate.

A. May perchlorate have an adverse effect on the health of persons?

Yes, perchlorate may have adverse health effects. The perchlorate anion is biologically significant specifically with respect to the functioning of the thyroid gland. Perchlorate can interfere with the normal functioning of the thyroid gland by inhibiting the transport of iodide into the thyroid, resulting in a deficiency of iodide in the thyroid. Perchlorate inhibits (or blocks) iodide transport into the thyroid by chemically competing with iodide, which has a similar shape and electric charge. The transfer of iodide from the blood into the thyroid is an essential step in the synthesis of thyroid hormones. Thyroid hormones play an important role in the regulation of metabolic processes throughout the body and are also critical to developing fetuses and infants, especially for brain development. Because the developing fetus depends on an adequate supply of maternal thyroid hormones for its central nervous system development during the first and second trimester of pregnancy, iodide uptake inhibition from perchlorate exposure has been identified as a concern in connection with increasing risk of neurodevelopmental impairment in fetuses of pregnant women with low dietary iodine. Poor iodide uptake and subsequent impairment of the thyroid function in pregnant and lactating women have been linked to delayed development and decreased learning capability in their infants and children (NRC, 2005). Therefore, the EPA continues to find that perchlorate may have an adverse effect on the health of persons.

B. Is perchlorate known to occur or is there a substantial likelihood that perchlorate will occur in public water systems with a frequency and at levels of public health concern?

The EPA has determined that perchlorate does not occur with a frequency and at levels of public health concern in public water systems. The EPA has made this determination by

comparing the best available data on the occurrence of perchlorate in public water systems to potential MCLGs for perchlorate.

In past regulatory determinations, the EPA has identified HRLs as benchmarks against which the EPA compares the concentration of a contaminant found in public water systems to determine if it occurs at levels of public health concern. For the 2011 regulatory determination the EPA identified potential HRLs values ranging from 1 to 47 µg/L for 14 different life stages. These HRLs were not final decisions about the level of perchlorate in drinking water that is without adverse effects. For the 2019 proposal, the EPA derived three potential MCLGs for perchlorate of 18, 56, and 90 µg/L for the most sensitive life stage using the best available peer reviewed science in accordance with the SDWA. After considering public comment, the EPA used these potential MCLGs as the levels of public health concern in assessing the frequency of occurrence of perchlorate in this regulatory determination. These MCLGs were set at levels to avoid IQ decrements of 1, 2, and 3 points respectively in the most sensitive life stage, the children of hypothyroxinemic women with low iodine intake. The EPA proposed an MCLG of 56 µg/L and alternative MCLG values of 18 and 90 µg/L.

The rationale used in deriving the numerical values is presented in greater detail in the EPA's technical support document titled "Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (USEPA, 2019b).

The EPA compared these potential MCLG values to the updated perchlorate UCMR 1 occurrence data set. A comprehensive description of the perchlorate occurrence data is presented

in Section VI of the 2019 proposal. It is also available in the "Perchlorate Occurrence and Monitoring Report" (USEPA, 2019a).

The occurrence data for perchlorate were collected from 3,865 PWSs between 2001 and 2005 under the UCMR 1. In the 2019 proposal, the EPA modified the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions in California and Massachusetts, which have enacted perchlorate regulations since the UCMR 1 data were collected. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 μg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public

Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states are now required to keep perchlorate levels in drinking water below their state limits. As discussed below, the EPA finds that perchlorate levels in drinking water and sources of drinking water have decreased since the UCMR 1 data collection. The main factors contributing to the decrease in perchlorate levels are the promulgation of drinking water regulations for perchlorate in California and Massachusetts and the ongoing remediation efforts in the state of Nevada to address perchlorate contamination in groundwater adjacent to the lower Colorado River upstream of Lake Mead.

To update the occurrence data for systems sampled during UCMR 1 from California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California

(https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

The EPA has determined that the UCMR 1 data with these updates are the best available data collected in accordance with accepted methods regarding the frequency and level of perchlorate nationally. The UCMR 1 data are from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the potential MCLG thresholds. The maximum measurements indicate highest perchlorate levels reported in at least one quarterly sample from surface water systems and at least one semi-annual sample from ground water systems.

Table 1: Perchlorate Occurrence and Exposure (Updated UCMR 1 Data Set)

Threshold Concentration (µg/L)	Entry Points with Detections above Threshold	Water Systems with Detections above Threshold	Percent of U.S. Water Systems with Detections above Threshold	Population Served
18 µg/L	17	15	0.03 %	620,560
56 µg/L	2	2	0.004 %	32,432
90 µg/L	1	1	0.002 %	25,972

Table 1 presents the number and percentage of water systems that reported perchlorate at levels exceeding the three proposed MCLG threshold concentrations. In summary, the updated perchlorate occurrence information suggests that at an MCLG of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the threshold, at an MCLG of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the threshold, and finally one system would exceed the MCLG threshold of 90 µg/L. Based on the analysis of drinking water occurrence presented in the 2019 proposal and the data summarized in Table 1 and the range of potential MCLGs, the EPA concludes that perchlorate does not occur with a frequency and at levels of public health concern in public water systems.

While the EPA has made its conclusion that perchlorate does not occur at a frequency and at levels of public health concern in public water systems based on the updated UCMR 1 data, the EPA also sought to find additional information about the perchlorate levels at the 15 water systems that had at least one reported result greater than 18 µg/L in the updated UCMR 1 data. The EPA found that perchlorate levels have been reduced at many of these water systems. Although these water systems were not required to take actions to reduce perchlorate in drinking water, many had conducted additional monitoring for perchlorate and found decreased levels or had taken mitigation efforts to address perchlorate, confirming the EPA's conclusion described above. The status of each of these systems is described in Table 2 below.

Table 2: Update on Systems with Perchlorate levels above 18 µg/L in the UCMR 1

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
Florida	Sebring Water	ND-70	The EPA contacted the Sebring system in January 2020. Operations personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
Florida	Manatee County Utilities Dept	ND-30	Researchers contacted the system to identify the source of perchlorate. System personnel attributed the sole perchlorate detection under UCMR 1 to analytical error. System personnel indicated that three other quarterly samples collected under UCMR 1 as well as other subsequent perchlorate sampling efforts were non-detect. Source: AWWA (2008)
Georgia	Oconee Co.-Watkinsville	38 (single sample)	Researchers contacted the system and found that a perchlorate contaminated well was removed from service in 2003. The system indicates that perchlorate is no longer detected. Source: Luis et al. (2019)
Louisiana	St. Charles Water District 1 East Bank	ND-24	The EPA was not able to identify updated data on perchlorate levels for this system.
Maryland	City of Aberdeen	ND-19	The system's 2018 Consumer Confidence Report (CCR) indicates that perchlorate was not detected. According to the Maryland Department of Environment, perchlorate was not detected in this system in 2019. In addition, researchers contacted the system and found that there has been no detection of perchlorate since treatment was installed in 2009. Source: Luis et al. (2019)
Maryland	Chapel Hill - Aberdeen Proving Grounds	ND-20	The EPA contacted the Chapel Hill System in January 2020. Water system personnel indicate that the Chapel Hill WTP was taken off-line and was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
			also indicate that monitoring was conducted in November 2019 and perchlorate was not detected in either the source well water or the finished water. In addition, according to the Maryland Department of Environment, perchlorate was not detected in this system in 2019.
Mississippi	Hilldale Water District	ND-20	The EPA contacted the Hilldale System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
New Mexico	Deming Municipal Water System	15-20	Data from the EPA's SDWIS/FED database indicates that the entry point that reported detections in UCMR 1 (Well #3) is now inactive (i.e., the contaminated source is no longer in use).
Nevada	City of Henderson	6-23	Researchers report that the perchlorate levels described in the system's CCR ranged from non-detect to 9.7 µg/L. Source AWWA (2008).
Ohio	Fairfield City PWS	6-27	The EPA contacted the Fairfield City System in January 2020. Water system personnel indicated that follow-up monitoring was conducted after UCMR 1, between 2002 and 2004. The Ohio EPA provided copies of the follow-up monitoring results which indicate that results at the entry point ranged from non-detect to 13 µg/L.
Ohio	Hecla Water Association-Plant PWS	ND-32	The EPA contacted the Hecla Water Association System in January 2020. Water system personnel indicated that that no follow-up/updated monitoring data for perchlorate are available.
Oklahoma	Enid	ND-30	The EPA reviewed Oklahoma's monitoring data and did not find any monitoring results reported for perchlorate.

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
Pennsylvania	Meadville Area Water Authority	ND-33	The EPA contacted the Meadville System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
Puerto Rico	Utuado Urbano	ND-420	The EPA contacted the Puerto Rico Aqueduct and Sewer Authority (PRASA) in January 2019. PRASA personnel indicated that no updated monitoring data for perchlorate are available. *NOTE: The PRASA personnel stated that the Utuado water system was significantly impacted by hurricane Maria and monitoring records from years prior to 2017 were lost.*
Texas	City of Levelland	ND-32	Researchers found that a water storage tank was the source of perchlorate contamination, the wells feeding the tank were tested by the state and perchlorate was not detected. The water tank was shut off from service. Source: Luis et al. (2019).

** - Values have been rounded. ND describes a sampling event where perchlorate was not detected at or above the UCMR 1 minimum reporting level of 4 µg/L. UCMR 1 results collected between 2001 and 2005.

++ - To obtain updated data and/or information regarding perchlorate levels, the EPA reviewed Consumer Confidence Reports and other publicly available data, as well as published studies. In addition, the EPA contacted some water systems for information about current perchlorate levels. (USEPA, 2020b)

C. Is there a meaningful opportunity for the reduction of health risks from perchlorate for persons served by public water systems?

The EPA's analysis presented in the 2019 proposal demonstrates that a NPDWR for perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. As discussed above, the EPA found that perchlorate occurs with

very low frequency at levels of public health concern. Based on updated UCMR 1 occurrence information, there were 15 water systems (0.03% of all water systems in the U.S.) that detected perchlorate in drinking water above the lowest proposed alternative MCLG of 18 µg/L and only 1 system had a detection above the proposed alternative MCLG of 90 µg/L. Specifically, Table 1 presents the population served by PWSs that were monitored under UCMR 1 for which the highest reported perchlorate concentration was greater than the identified thresholds. The EPA estimates[2] that the number of people who may be potentially consuming water containing perchlorate at levels that could exceed the levels of concern for perchlorate could range between 26,000 and 620,000. The small number of water systems with perchlorate levels greater than identified thresholds and the corresponding small population served provides ample support for the EPA's conclusion that the regulation of perchlorate does not present a "meaningful opportunity for health risk reduction for persons served by public water systems," within the meaning of the SDWA, section 1412(b)(1)(A)(iii).

The EPA also considered the findings of the Health Risk Reduction and Cost Analysis (HRRCA, USEPA 2019c) as additional information supporting withdrawal of the regulatory determination. The HRRCA for perchlorate (which was presented in the 2019 proposal) provides a unique set of economic data indicators that are not available for regulatory determinations

[2] The values shown in Table 1 are based on the revised UCMR 1 data. The EPA also applied statistical sampling weights to the small systems results to extrapolate to national results. There was one small system included in the statistical sample stratum which had a perchlorate measurement exceeding 18 µg/L. Accordingly, the EPA estimates that approximately 41,000 small system customers may be exposed to perchlorate greater than 18 µg/L.

because the HRRCA is required for a proposed NPDWR under SDWA Section 1412(b)(3)(C), but is not required to support a regulatory determination. Accordingly, because the EPA initially determined that perchlorate met the criteria for regulation and began the regulatory analysis process, the HRRCA was available with respect to perchlorate, and the Agency considered this comprehensive economic analysis in informing its decision to withdraw the regulatory determination.

Specifically, the HRRCA provides a description of the potential benefits and costs of a drinking water regulation for perchlorate. For all potential regulatory levels considered for perchlorate (18, 56, and 90 µg/L) the total costs associated with establishing a regulation were substantially higher than the potential range of benefits. The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the states, while having little impact on health risk reductions and the associated low estimates of benefits.

Based on a comparison of costs and benefits estimated at the three potential regulatory levels, the EPA determined in the 2019 proposal that the benefits of establishing a drinking water regulation for perchlorate do not justify the potential costs.

A drinking water regulation for perchlorate would impose significant burden on states and water systems, mainly associated with requirements for monitoring but which would result in very few systems having to take action to reduce perchlorate levels. It is of paramount importance that water systems (particularly medium, small and economically distressed systems)

focus their limited resources on actions that ensure compliance with existing NPDWRs and maintain their technical, managerial, and financial capacity to improve system operations and the quality of water being provided to their customers rather than spending resources monitoring for contaminants that are unlikely to occur.

D. What is the EPA's final regulatory determination on perchlorate?

Based on the EPA's analysis of the best available public health information, and after careful review and consideration of public comments on the June 2019 proposal, the Agency is withdrawing its 2011 determination and is making a final determination to not regulate perchlorate. Accordingly, the EPA will not issue a NPDWR for perchlorate at this time. While the EPA has found that perchlorate may have an adverse effect on human health, based on the analysis presented in this notice and supporting record, the EPA has determined that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and that regulation of perchlorate does not present a meaningful opportunity to reduce health risks for persons served by public water systems. This conclusion is based on the best available peer reviewed science and data collected in accordance with accepted methods on perchlorate health effects and occurrence.

IV. Summary of Key Public Comments on Perchlorate

The EPA received approximately 1,500 comments from individuals or organizations on the June 2019 proposal. This section briefly discusses the key technical issues raised by commenters and the EPA's response. Comments are also addressed in the ''Comment Response

Document for the Final Regulatory Action for Perchlorate'' (USEPA, 2020a) available at http://www.regulations.gov (Docket ID No. EPA–HQ–OW–2018–0780).

A. SDWA Statutory Requirements and the EPA's Authority

The EPA received comments stating the Agency should promulgate an MCLG and MCL for perchlorate and comments stating the Agency should not promulgate a regulation. After considering these comments the EPA has re-evaluated perchlorate in accordance with the SDWA, section 1412(b)(1)(A), which requires that the Agency promulgate a NPDWR if (i) the contaminant may have an adverse effect on the health of persons; (ii) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (iii) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The EPA has determined, based upon the best available peer reviewed science and data collected in accordance with accepted methods, that perchlorate does not occur at a frequency and at levels of public health concern, and that regulation of perchlorate does not present a meaningful opportunity for health risk reduction. Because perchlorate does not meet the statutory criteria for regulation, the EPA lacks the authority to issue a MCLG or NPDWR for perchlorate, and is therefore withdrawing its 2011 regulatory determination and issuing this final determination to not regulate perchlorate. For more information regarding EPA's statutory authority to withdraw its regulatory determination, see Section II.C above.

B. *Health Effects Assessment*

Health Effects/MCLG Derivation

The EPA received comments indicating that the Agency should utilize different approaches to derive the MCLG for perchlorate including approaches that some states used to develop their perchlorate advisory levels or drinking water standards. The EPA considered a number of alternative approaches to develop the MCLG for perchlorate and in accordance with the SDWA, section 1412(e), the Agency sought recommendations from the Science Advisory Board. The EPA derived the proposed MCLG for perchlorate based on the approach recommended by the Science Advisory Board (SAB) (SAB for the U.S. EPA, 2013). The SAB recommended that *"the EPA derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters."* The EPA has implemented these recommendations and has obtained two independent peer reviews of the analysis. These peer reviewers stated that: "*Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments below, the current models are fit-for-purpose to determine an MCLG*" (External Peer Reviewers for USEPA, 2018, p. 2).

The EPA received comments indicating the most sensitive life stages were not selected and/or considered in the Agency's approach. The EPA disagrees. Gestational exposure to perchlorate during neurodevelopment is the most sensitive time period. The NRC concluded that the population most sensitive to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. In addition, there is clear evidence that disrupted maternal thyroid hormone levels during gestation can impact neurodevelopment later in life (Alexander et al., 2017; Costeira et al., 2011; Endendijk et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016; Morreale de Escobar, Obregón, & Escobar del Rey, 2004; Noten et al., 2015; Pop et al., 2003, 1999;

SAB for the U.S. EPA, 2013; Thompson et al., 2018; van Mil et al., 2012; Wang et al., 2016; Zoeller & Rovet, 2004; Zoeller et al., 2007). The available data demonstrate that the fetus of the first trimester pregnant mother, when compared to other life-stages, experiences the greatest impact from the same dose of perchlorate, which is described in detail in Section 6 of the document "Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (USEPA, 2019a). Some commenters suggested that the bottle-fed infant is a more sensitive life-stage. The EPA disagrees as described in the January 2017 Peer Review Report on the original Biologically Based Dose Response (BBDR) model, the bottle-fed infant's thyroid hormone levels were not impacted by doses of perchlorate up to 20 µg/day (External Peer Reviewers for USEPA, 2017). This lack of any impact is due primarily to the iodine in the formula, which offsets the impact of perchlorate on the thyroid.

The EPA received comments advocating for the use of the population-based approach evaluating the shift in the proportion of a population that would fall below a hypothyroxinemic cut point under a perchlorate exposure scenario. The EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of a MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. In addition, the fact that thyroid hormone levels vary by reference population and that there is not a defined value representing

hypothyroxinemia makes the population-based approach less desirable than the approach selected (USEPA, 2018).

End Point Selection/Basis

The EPA received comments regarding the magnitude of an IQ change which should be used in deriving the MCLG. The EPA's proposed MCLG was based upon avoiding a 2% change in IQ in the most sensitive life stage and the EPA also requested comment on alternative options for the MCLG that would respectively avoid 1% or 3% change in IQ in the most sensitive life stage. Many comments stated that the EPA should at most consider a 1% IQ change. However, several commenters stated a 3% change is too small to have a meaningful impact and suggested the EPA consider a higher IQ percent change.

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 % extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint.

Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, ''[a]

BMR of 1% has typically been used for quantal human data from epidemiology studies'' (p. 21, USEPA, 2012). For the specific context of setting an MCLG for perchlorate, the EPA evaluated the level of perchlorate in water associated with a 1% decrease, a 2% decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points).

In evaluating the frequency and level of occurrence of perchlorate in drinking water the EPA has found that perchlorate does not occur with frequency even at the lowest alternative MCLG of 18 µg/L which is based upon avoiding a 1% change in IQ in the most sensitive life stage.

The EPA received comments that the proposed MCLG did not incorporate an adequate margin of safety to comply with the SDWA. The EPA disagrees that it failed to use an adequate margin of safety. The EPA's assessment focused upon the most sensitive subset of the population, specifically offspring whose mothers had low (75 µg/day) iodine intake and were hypothyroxinemic (fT4 in the lowest 10th percentile of the population). In addition, to account for uncertainties and to ensure the most sensitive subset of the population is protected with an adequate margin of safety, a 3-fold uncertainty factor was applied to the proposed MCLG calculation (USEPA, 2019a). More discussion on the uncertainty factor is presented in the section "Consideration of Uncertainties."

The EPA received some comments stating that the selection of the study for informing the relationship between maternal hormone levels (fT4) and IQ was inadequately described. Other comments supported the EPA's study selection. The EPA concludes that

selection of the Korevaar et al. (2016) study is appropriate because that study provides the most robust data available with a clear measure of neurodevelopment that can be expressed as a function of changing maternal fT4 exposure, which is necessary to the development of the model.

BBDR and PBPK Models

The EPA received comments indicating the BBDR model was not transparent, scientifically valid, or based on robust data. The EPA disagrees. The model represents the best available peer reviewed science and uses the best available data to inform a MCLG for perchlorate. The EPA does not believe there is a significant lack of transparency with respect to the assumptions related to the BBDR model. Appendix A of the EPA's Proposed MCLG Approaches report outlines the justification for all assumptions used in the development of the BBDR model (USEPA, 2019a). The EPA also disagrees with the assertion the BBDR model is far too uncertain to be relied upon as the basis for the derivation of the RfD. The EPA has used the best available science to calibrate the pharmacokinetic aspects of the BBDR model. The development of the BBDR model was in response to SAB recommendations and a model was deemed to be a more refined approach to estimating a dose-response relationship between perchlorate exposure and maternal fT4 than anything that was available in the current scientific literature. The EPA disputes the claim that there are issues with the scientific validity of the BBDR model as the Agency conducted a peer review

of the approach proposed and the reviewers stated the approach was "fit for purpose" to inform a MCLG for perchlorate (External Peer Reviewers for U.S. EPA, 2018, p. 2).

Consideration of Uncertainties

The EPA received comments on the Agency's use of Uncertainty Factors (UFs); with most commenters suggesting that the EPA should consider a higher UF. The EPA thoroughly considered the application of UFs when deriving the RfDs and followed guidance presented in "A review of the reference dose and reference concentration processes" (USEPA, 2002). The EPA concluded that the UFs are adequately justified and subsequently no changes have been made. Justification for each of the UFs can be found in Section 11 of the Agency's MCLG Derivation report (USEPA, 2019a).

The EPA selected a UF of 3 for inter-individual variability because the Agency specifically modeled groups within the population that are identified as likely to be at greater risk of the adverse effects from perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother). The EPA selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake). As discussed in the MCLG Derivation report, the EPA has attempted to select the most appropriate inputs to protect the most sensitive population with an adequate margin of safety (USEPA, 2019a). The EPA has determined that the selection of a UF of 3 for inter-individual variability is justified. As described in the MCLG Derivation report, because the output from the BBDR model is specific to the sensitive population the EPA concluded that

the UF of 3 is appropriate. In regards to variation in sensitivity among the members of the human population (i.e., inter-individual variability), section 4.4.5.3 of the EPA guidance "A review of the reference dose and reference concentration process" (USEPA, 2002) document states, "In general, the Technical Panel reaffirms the importance of this UF, recommending that reduction of the intraspecies UF from a default of 10 be considered only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s). Similar to the interspecies UF, the intraspecies UF can be considered to consist of both a toxicokinetic and toxicodynamic portion (i.e. 10^0.5 each)" (USEPA, 2002). Given that the BBDR model significantly accounts for differences within the human population, the full UF of 10 is not warranted.

One commenter suggested using a UF greater than 1 to account for the extrapolation of the lowest-observed adverse effect level (LOAEL) to the no-observed-adverse-effect-level (NOAEL). LOAELs and NOAELs were not identified or used by the EPA in its assessment because the Agency employed a sophisticated BBDR modeling approach, which was coupled with extrapolation to changes in IQ using linear regression, to determine a POD that would not be expected to represent an adverse effect. Therefore, a UF of 1 is appropriate. Other commenters suggested incorporating UFs for database deficiencies. Based on the findings of the NRC report, the EPA has previously concluded that this UF was not needed for deficiencies in the perchlorate database (NRC, 2005; USEPA, 2005a). The EPA believes that

a UF of 1 to account for database deficiencies is still appropriate given that the state of the perchlorate database has only increased since 2005.

C. *Occurrence Analysis*

The EPA received comments suggesting that the revised UCMR 1 data did not provide an adequate estimate of the perchlorate occurrence in drinking water systems. Some commenters indicated that the age of the collected data rendered the occurrence analysis obsolete and overestimated, since it no longer captures current lower contamination conditions that have been achieved due to mitigation measures taken in the Colorado River Basin. Other commenters criticized the EPA for replacing UCMR 1 data with compliance data for the States of California and Massachusetts.

The EPA recognizes that changes in perchlorate levels (increasing or decreasing) may have occurred in water systems since the UCMR 1 samples were collected between 2001 to 2005. The EPA updated the UCMR 1 data set to improve its accuracy in representing the current conditions for states that have enacted perchlorate regulations since the UCMR 1 monitoring was conducted. As outlined in the June 26, 2019 proposal, the EPA updated occurrence data for California and Massachusetts with current compliance data as reported by the states. Systems from these two states that were sampled during the UCMR 1 and that had reported perchlorate detections were updated with more recently measured values taken from current compliance monitoring data from Consumer Confidence Reports and state-level

perchlorate compliance monitoring data to match corresponding water systems and entry points.

The EPA has determined that the updated UCMR 1 data are the best available data collected in accordance with accepted methods on the frequency and level of perchlorate occurrence in drinking water on a national scale.

V. Conclusion

With this withdrawal of the 2011 perchlorate regulatory determination and final determination to not regulate perchlorate, the EPA announces that there will be no NPDWR for perchlorate at this time. The EPA could consider re-listing perchlorate on the CCL and could proceed to regulation in the future if the occurrence or health risk information changes. As with other unregulated contaminants, the EPA will consider addressing limited instances of elevated levels of perchlorate by working with the affected system and state, as appropriate.

VI. References

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List of Subjects in 40 CFR Parts 141 and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew Wheeler,

Administrator.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF WATER

MEMORANDUM

SUBJECT: *Federal Register* Notice of Final Action on Perchlorate

FROM: Jennifer L. McLain, Director
Office of Ground Water and Drinking Water

JENNIFER MCLAIN Digitally signed by JENNIFER MCLAIN Date: 2020.05.19 12:21:18 -04'00'

TO: David P. Ross
Assistant Administrator

Attached for your approval and transmittal to the Office of Policy for initiation of interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate."

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available science.

I recommend that you approve and transmit the attached notice to the Office of Policy to initiate Interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

Message

From: Wadlington, Christina [Wadlington.Christina@epa.gov]
Sent: 10/10/2017 12:27:49 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]
Subject: RE: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

Updated based on Steph's recent email.
Please let me know if you have any questions.

RELEASE SCHEDULE
October 6, 2017 (Completed)

- SRMD informally notifies requestors via phone call (Eric)
- OGC notifies NRDC (via phone call) (Eric)
- OGWDW/SRMD notification of Regional Contacts (Christina)
- SRMD notification of federal partners (FDA, ATSDR, NIEHS, OMB) (Eric)
- OPA notification of Regional PADS and federal agencies' (OW comms)

October 11, 2017

8:00 a.m OGWDW stakeholder heads up (Peter/Jennifer emails)
9:00 a.m OCIR Congressional heads up emails (Matt)
10:00 p.m Website goes live (Russ/Christina)
Broader congressional notifications (emails with link to website) (OCIR)

**** Send formal notification letters to requestors once available**

From: Burneson, Eric
Sent: Friday, October 06, 2017 3:28 PM
To: Wadlington, Christina <Wadlington.Christina@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: RE: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

I just spoke with three of the people requesting extensions of the deadlines:
AWWA – Kevin Morely
Perchlorate Study Group - Tom Roberts
Chlorine Institute – Erica Bernstein

I left a message with
American Chemistry Council – Mark Gibson

And I left a message with
NRDC – Erik Olson explaining that we would be extending the deadline(after consulting with Carrie Wehling).

From: Wadlington, Christina
Sent: Friday, October 06, 2017 3:02 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

Did SRMD want to touch base with OGC or did you want me to? Happy with either.

From: Flaharty, Stephanie
Sent: Friday, October 06, 2017 2:57 PM
To: Wadlington, Christina <Wadlington.Christina@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material
Importance: High

Thanks !

From: Wadlington, Christina
Sent: Friday, October 06, 2017 2:55 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Question on roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

Afternoon,

Please find an updated roll out. We can start the notifications asap.

**

RELEASE SCHEDULE
October 6, 2017

- SRMD informally notifies requestors via phone call (Eric)
- OGC notifies NRDC (via phone call) (Dawn)
- OGWDW/SRMD notification of Regional Contacts (Christina/Lisa)
- SRMD notification of federal partners (FDA, ATSDR, NIEHS, OMB)
- OPA notification of Regional PADS and federal agencies' (OW comms)

Release Day (when publically available on FR site; public inspection day)

8:00 a.m	OGWDW stakeholder heads up (Peter/Jennifer emails)
10:00 a.m	OCIR Congressional heads up emails (Matt)
11:00 p.m	Website goes live (Russ/Christina)
	Broader congressional notifications (emails with link to website) (OW Comms)

**** Send formal notification letters to requestors once available**

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 5/19/2020 10:40:43 PM
To: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]
Subject: FOR REVIEW: draft perchlorate response to comment document
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-19-20 v2.docx

DRAFT/DELIBERATIVE
Hello Jennifer,
Attached for your is the draft perchlorate response to comment document. Please let us know if you have questions or concerns.
Thanks,
Lisa

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 6/9/2020 5:10:31 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: Request for Input - Perchlorate RtC
Attachments: Perchlorate Draft Comment Response Document 6-9-20 v1.docx

Hi Eric,

We have completed the edits/revisions to the Perchlorate Response to Comment Document. I am attaching a copy of it here in case we are asked for it.

I have our contractor currently working on making only formatting edits to the document, so it is ready for publication and for upload to the docket next week.

Let me know if you have any questions.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, June 09, 2020 8:55 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Request for Input - Perchlorate RtC

Sam:
Either here or in one of the other responses referenced we should write that EPA and state remediation activities are informed by a number of potential applicable or relevant and appropriate requirements other than national primary drinking water regulations. Additionally the Safe Drinking Water Act's criteria for establishing National Primary Drinking Water Regulations does not include consideration of cleanup standards for contaminated sites.

From: Hernandez-Quinones, Samuel
Sent: Tuesday, June 09, 2020 6:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Request for Input - Perchlorate RtC

Hi Eric,

I had a question for you about a comment from Jenifer on the RtC document. Specifically, she had a question on comments #1.16 & #1.11. These comments have to do claims about how mitigation measures could be affected in the absence of a perchlorate regulation.

We had come up with a response that generally addressed the issue, but it seems like Jenifer would like a more direct response. I need some assistance from you in coming up with a response for these comments.

See below:

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water

Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Grevatt, Peter [Grevatt.Peter@epa.gov]
Sent: 11/20/2017 9:40:09 PM
To: KMorley@awwa.org
CC: Tracy Mehan [tmehan@awwa.org]; svia@awwa.org; Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Shapiro, Mike [Shapiro.Mike@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]
Subject: FW: AWWA perchlorate MCLG comments_11.20.17.pdf
Attachments: AWWA perchlorate MCLG comments_11.20.17.pdf

Thanks Kevin. I appreciate your giving us a heads up on AWWA's comments!

From: Kevin Morley [mailto:KMorley@awwa.org]
Sent: Monday, November 20, 2017 4:33 PM
To: Shapiro, Mike <Shapiro.Mike@epa.gov>
Cc: Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tracy Mehan <tmehan@awwa.org>; svia@awwa.org
Subject: AWWA perchlorate MCLG comments_11.20.17.pdf

Please accept the attached comments from AWWA regarding the proposed MCLG approach for perchlorate.

Sent on behalf of G. Tracy Mehan, III.

Kevin M. Morley, PhD
American Water Works Association
Manager, Federal Relations
1300 Eye Street, NW Suite 701W
Washington, DC 20005
D: 202-326-6124

This communication is the property of the American Water Works Association and may contain confidential or privileged information. Unauthorized use of this communication is strictly prohibited and may be unlawful. If you have received this communication in error, please immediately notify the sender by reply email and destroy all copies of the communication and any attachments.

American Water Works Association
Dedicated to the World's Most Important Resource ®

Message

From: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Sent: 5/14/2020 2:54:19 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: FOR REVIEW: draft perchlorate action and transmittal memos
Attachments: Transmittal Memo JM to DR 5-13-20 v1.SF.docx; Perchlorate Action Memo 5-13-2020_.SF.docx

Hi Lisa,

The attached drafts reflect formatting edits (Dave's preferences and OP's template).

I noted in the Action Memo file that the updated section, now titled "STAKEHOLDER INVOLVEMENT and ANTICIPATED RESPONSE," prompts the lead office to discuss any *stakeholder involvement that occurred during development of the action*.

Thanks for checking...

Best,
Steph

From: Flaharty, Stephanie
Sent: Thursday, May 14, 2020 7:55 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: FOR REVIEW: draft perchlorate action and transmittal memos

Good Morning Lisa,

I'm going to have quite a few edits (per Dave's preferred format) and will send you the drafts a bit later this morning.

Thanks,
Steph

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, May 13, 2020 4:25 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Subject: RE: FOR REVIEW: draft perchlorate action and transmittal memos

Lisa:
Attached please find my suggested edits to the Perchlorate transmittal memo and action memo. I modified the memos to reflect our status of submission to OMB for Interagency review.
I am copying Stephanie so that she may provide any additional edits to assure consistency with Agency templates.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water

U.S. Environmental Protection Agency
202 564 5250

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, May 06, 2020 3:51 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FOR REVIEW: draft perchlorate action and transmittal memos

DRAFT DELIVERABLE
Hi Eric,
For you review are the draft memos to accompany the perchlorate final action. Please let us know if you have question, concerns or need more information.
Thanks,
Lisa

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Regulatory Determination on Perchlorate

FROM: Jennifer L. McLain~~,~~
~~-~~Director,
Office of Ground Water and Drinking Water

TO: David P. Ross
Assistant Administrator~~, Office of Water~~

Attached for your approval and transmittal to the Office of ~~-~~Policy for initiation of ~~I~~inter-~~A~~agency ~~R~~review ~~the Administrator~~ is a *Federal Register* notice titled: "Notice of Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Regulatory Determination on Perchlorate."

On February 11, 2011, the EPA published a final determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published ~~a~~the proposed ~~N~~National ~~P~~Primary ~~D~~Drinking ~~W~~Water ~~R~~Regulation ~~(NPDWR)~~ for ~~p~~Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 ~~r~~Regulatory ~~d~~Determination to regulate perchlorate. The ~~Agency~~EPA received approximately 1,500 comments on the proposed rule. In ~~T~~the attached notice, the EPA ~~concludes, based upon consideration of public comments and the best available information, that the Agency~~ is withdrawing the 2011 ~~r~~Regulatory ~~d~~Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.~~;~~

~~On June 26, 2019 (84 FR 30524), the EPA published a proposed National Primary Drinking Water Regulation (NPDWR) for perchlorate and requested public comment on multiple alternative regulatory actions, including the alternative of withdrawing the 2011 regulatory determination for perchlorate. The Agency received approximately 1,500 comments on the proposed rule. In consideration of public comments and based on the best available human health and occurrence information, the Agency is withdrawing the 2011 regulatory determination and is making a final determination not to regulate perchlorate by publication of this *Federal Register* notice.~~

~~In determining whether to regulate a contaminant, the EPA must follow the criteria mandated by the 1996 Safe Drinking Water Act (SDWA) Amendments. Specifically, in order to issue a MCLG and NPDWR for perchlorate, the EPA must determine that perchlorate "may have an adverse effect on the health of persons," that perchlorate occurs at "a frequency and at levels of public health concern" in public water systems, and that regulation of perchlorate in drinking water systems "presents a~~

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~~meaningful opportunity for health risk reductions for persons served by public water systems." SDWA 1412(b)(1)(A). Based on the EPA's new analysis and after careful review and consideration of public comments on the June 2019 proposal, the Agency is withdrawing its 2011 determination and is now making a determination not to regulate perchlorate. While the EPA has found that perchlorate may have an adverse effect on human health, the EPA has determined that perchlorate does not occur in public water systems at a frequency and at levels of public health concern and regulation of perchlorate does not present a meaningful opportunity to reduce health risks for persons served by public water systems. This conclusion is based on the best available peer reviewed science and data collected in accordance with accepted methods on perchlorate health effects and occurrence. Accordingly, the EPA will not issue a NPDWR for perchlorate.~~

~~The EPA maintains the authority to re-list perchlorate on the Contaminant Candidate List (CCL) and proceed with regulating perchlorate in the future if occurrence or risk information changes to warrant this. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the affected system and state, or issuing a health advisory under the SDWA Section 1412(b)(1)(F), as appropriate. In addition, the EPA can also address the limited instances of perchlorate occurrence by working with the states and health assessment authorities under SDWA Section 1431, as appropriate.~~

I recommend that you approve and transmit the attached notice to the Office of Policy to ~~transmit the attached notice to the~~initiate the Office of Management and Budget's ~~for Inter-Agency R~~interagency review, in accordance with Executive Order 12866, ~~the Administrator for review.~~ If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

~~Federal Register Notice~~
~~Draft Action Notice~~

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Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 5/18/2020 9:34:09 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: FW: Notice of Final Action on Perchlorate
Attachments: Perchlorate Action Memo 5-18-20.cb.docx; Draft Perchlorate Final Action FRN 5-18-20 v1 Redline.cb.docx

Eric – please let me know if you want to discuss.

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Monday, May 18, 2020 5:29 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Thanks – couple of bubble box questions and then I had one redline edit I added to the Notice.

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Monday, May 18, 2020 3:01 PM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Charlotte – as agreed, I'm sending you the draft final perchlorate FRN for review. The redline includes the changes made since the FAR. I'm also including the draft Action Memo. Please let us know if your preference is to have these submitted to OW through CMS now or after you have reviewed. Let me know if you want to talk.

Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 2:48 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Jennifer:

Attached for transmission to OW are revised versions of the FRN for the Perchlorate Final Action. There is both a clean and track changes version that includes edits made since initiating FAR (including the edits you asked for on Saturday and adding 3 more SAB recommendations to page 14 that were in the proposal but were not included in the draft we provided you on Friday). Also please find clean version of the transmittal memo from you to Dave Ross and the Action memo incorporating your edits.

Please note that there is also a redline version of the Action Memo for you to see the responses to your comments on the document. I do not recommend transmitting that memo to OW.

Eric Burneson, P.E.
Director of Standards and Risk Management

Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, May 18, 2020 2:18 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Attached are the revised Redline and Clean versions of the Perchlorate FR Notice. Once we are ready for OP's submittal to OMB let me know and I will provide a version that adheres to OP's file name formatting guidelines.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 1:14 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Sam

1. Change the title please. This was requested by OGC at Sr. Leadership levels.
2. Provide the same level of detail on the SAB recommendations as was included in the proposal.
3. I don't think the HRRCA text is necessary and do not want to add it at this stage since there are OGC edits that already make this clear.

Eric

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, May 18, 2020 12:41 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Here is a revised Redline of the document (from FAR). We had a few questions/issues for your consideration about the attached file. Specifically:,

1- Page #1, Notice Tittle: We did not accept the edits to the notice tittle. Because, the tittle of the notice was specifically crafted by OGC to capture the multiple actions EPA is taking. Suggest consulting with OGC before modifying this tittle.
2- Page #14, SAB Recommendations: SAB provided 4 main recommendations in 2013 but we only listed the first recommendation. Please advise if we should list all 4 recommendations here or not.
3- Page #26, Missing HRRCA Text: This language was offered by TAB in its 5-13-20 version of the draft FRN, but it did not show up in the version provided by OGWDW with Eric's & Jennifer's comments. We have inserted the language here for the reviewer's consideration. Please advise if we should keep it.

Once you provide your feedback, I will modify the redline version and also provide a Clean copy for transmittal.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 8:42 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Lisa and Sam
Attached are Jennifer's comments and edits on the draft FRN. I have responded to her questions in the attached and made some additional edits. Can you please get a revised clean version and another redline version that compares this document and the version that was distributed to FAR?
Thanks for your work on this.
Eric

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Saturday, May 16, 2020 11:39 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Looks very good. See p. 6 for my only concern w/the revisions.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 15, 2020 5:03 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: Notice of Final Action on Perchlorate

Jennifer

Attached for your approval and transmittal to the Office of Water for their approval and transmittal to the Office Policy for initiation of interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate." Also attached for your review are a draft transmittal memo from you to the Assistant Administrator of Water, a draft Action Memorandum and a track changes version of the FR notice that denotes the changes made as a result of Final Agency Review.

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

I recommend that you approve and transmit the attached notice to the Office of Water for their review, approval and transmission to the Office of Policy to initiate interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Flowers, Lynn [Flowers.Lynn@epa.gov]
Sent: 5/29/2020 3:29:30 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: Inside EPA: Vanderbilt researchers find greater thyroid impacts from perchlorate
Attachments: 2020.5. NIS allosteric modulation.pdf

Eric: here is the paper. Looks like Nancy Carrasco served on the 2013 SAB panel.
Lynn

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Advisor, Policy and Engagement
Office of Research and Development
USEPA, Washington, DC
(ph)202-564-6293, (cell)202-834-8393

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 29, 2020 9:32 AM
To: Flowers, Lynn <Flowers.Lynn@epa.gov>
Subject: FW: Inside EPA: Vanderbilt researchers find greater thyroid impacts from perchlorate

Lynn
In addition to your questions about LCR sampling at 11, I will want to discuss this new study referenced in the article below.
Thanks
Eric

From: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Sent: Friday, May 29, 2020 7:57 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Corr, Elizabeth <Corr.Elizabeth@epa.gov>
Subject: Inside EPA: Vanderbilt researchers find greater thyroid impacts from perchlorate

Vanderbilt researchers find greater thyroid impacts from perchlorate

May 28, 2020

Tweet

Vanderbilt University researchers have published findings indicating the munitions ingredient perchlorate impedes thyroid function more significantly than previously thought, coming shortly after EPA signaled it was unlikely to regulate the substance in drinking water.

In a May 25 article published in the journal *Nature Structural & Molecular Biology*, Vanderbilt researchers found that perchlorate hampers the uptake of iodide, a key component of thyroid hormones, "in a more pronounced and fundamental way than commonly considered," according to an article [https://news.vanderbilt.edu/2020/05/26/new-research-reveals-environmental-pollutant-in-drinking-water-is-more-dangerous-than-previously-understood/] by Vanderbilt's research news website.

“The end effect of perchlorate exposure on thyroid hormones is that the transport of iodide is impaired,” Nancy Carrasco, the paper’s lead author and chair of Vanderbilt’s Department of Molecular Physiology and Biophysics, says in the article. “Much less iodide will be transported. Now that we understand exactly what perchlorate does, we can clearly see that contamination of drinking water with this chemical is more worrisome than previously thought,” she says in the article.

The findings come just as EPA has signaled it will likely pull back on regulating the chemical -- an ingredient in rocket fuel and munitions -- in drinking water. The agency is preparing to issue a final action in June regarding its 2019 proposal on how or whether to regulate perchlorate under the Safe Drinking Water Act (SDWA).

Earlier this month, EPA Administrator Andrew Wheeler noted that due to steps taken by EPA, states and public water systems to identify, monitor and mitigate perchlorate, “the levels have decreased in drinking water."

In a paper EPA released May 14, the agency says it “re-evaluated the available data on the frequency and level of perchlorate occurrence in public water systems,” comparing this new data with the lowest potential maximum contaminant level goal that the agency considered in its June 2019 proposed rule.

“The EPA concludes that there is infrequent occurrence of perchlorate at the levels of public health concern. In addition, studies show that perchlorate occurrence in the environment has decreased over time, due to several mitigation actions taken by the EPA and others,” it says.

The *New York Times* reported earlier this month that the agency has decided to finalize a rule that calls for no drinking water limits on the chemical. While EPA has not yet sent its final perchlorate drinking water regulatory determination to the White House Office of Management & Budget for review, the *Times* reported that, according to two EPA staff members, the administration will choose to “not impose any limits on perchlorate.”

A decision not to regulate the chemical in drinking water would be a second reversal on the issue, after the Obama administration in 2011 reversed the Bush administration’s 2008 decision to refrain from regulating the chemical. EPA’s signaled action is expected to draw litigation from environmentalists, who say it violates a court order.

In the Vanderbilt study, researchers found that “perchlorate exposure fundamentally alters the mechanism” by which a key protein found in thyroid cells “transports iodide into the thyroid, making it less efficient,” the university’s article says.

“Even what would be considered low concentrations of perchlorate significantly decrease iodide transport and the resulting production of thyroid hormones,” the article says. “Because of thyroid hormones’ outsize influence on human cognitive and physical development, the populations most vulnerable to perchlorate-contaminated drinking water are pregnant women, nursing women, developing fetuses, and newborn babies,” it says.

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 9/27/2017 8:24:40 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Request for Comment Period Extension: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water
Attachments: Chlorine Institute Request for Comment Period Extension.pdf

FYI – Chlorine Institute asking for same comment extension as PSG.

From: Hernandez-Quinones, Samuel
Sent: Wednesday, September 27, 2017 3:50 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: FW: Request for Comment Period Extension: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

Hi Lisa,

We received another request to extent the comment period. This time it is the Chlorine Institute, they request 45 additional days on the interim list & charge, and 75 additional days on the Draft Report. I will proceed to add this letter to the docket.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Erica Bernstein [mailto:EBernstein@cl2.com]
Sent: Wednesday, September 27, 2017 3:29 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Shapiro, Mike <Shapiro.Mike@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Request for Comment Period Extension: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

Good Afternoon Mr. Hernandez,

Please see the letter attached requesting a comment period extension on the "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" [EPA–HQ–OW–2016–0438] and on the "Interim List of Perchlorate in Drinking Water Expert Peer Reviewers and Draft Peer Review Charge Questions" [EPA-HQ-OW-2016-0439].

Thank you for your consideration.

Sincerely,

Erica Bernstein

Aim For Zero

Director - Outreach | 703.894.4114 *office* | 804.357.4758 *cell* | ebernstein@CL2.com | www.chlorineinstitute.org

THE CHLORINE INSTITUTE
1300 Wilson Boulevard, Suite 525, Arlington, VA 22209
Phone: 703-894-4140 Fax: 703-894-4130
www.chlorineinstitute.org

September 27, 2017

SUBMITTED VIA E-MAIL

Samuel Hernandez
U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

Re: Request for Comment Period Extension on the draft report entitled: "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" [EPA–HQ–OW–2016–0438] and on the "Interim List of Perchlorate in Drinking Water Expert Peer Reviewers and Draft Peer Review Charge Questions" [EPA-HQ-OW-2016-0439]

Dear Mr. Hernandez,

The Chlorine Institute (CI) respectfully requests that the Environmental Protection Agency (EPA) extend the comment deadline by an additional 75 days to January 13, 2018 on the *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water.*

Given the complexity of the revisions in the Biologically Based Dose-Response (BBDR) model and the impact it will have on our members, we do not believe 45 days is sufficient to effectively review the revisions to the BBDR model.

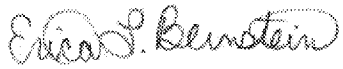
CI also requests that the EPA extend the public comment period on the *Interim List of Perchlorate in Drinking Water Expert Peer Reviewers and Draft Peer Review Charge Questions* by 45 days to November 20, 2017.

We would appreciate hearing EPA's response to this request as soon as possible, so that we can dedicate and manage our resources accordingly while continuing to conduct a thorough review and analysis of the *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water.*

ED_005043_00058478-00001

Should you have questions or would like to discuss this matter, please contact me by phone at 703-894-4114 or by email at ebernstein@CL2.com.

Sincerely,



Erica Bernstein
Director - Outreach
The Chlorine Institute
703.894.4114
ebernstein@CL2.com

CC:
Michael Shapiro – EPA, OW
Lee Forsgren – EPA, OW
Peter Grevatt – EPA, OGWDW
Eric Burneson – EPA, OGWDW

ED_005043_00058478-00002

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 3/17/2020 12:15:35 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents
Attachments: Perchlorate Recommendations for PWS_03.17.2020.docx; Perchlorate Reductions_03.17.2020.docx

Eric, please see the revised document attached. I noticed we were missing references we added on 2/28 so I put those back in the reductions document. I do not agree with a edit on page 2 (highlighted blue) stating POU protects the whole home. Let us know if you'd like additional changes.

Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 4:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Thanks. Can I get a revised by 8:30 am tomorrow morning?

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, March 16, 2020 3:42 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric,
I think they are mostly straight forward. If I recall we were asked previously for underlying data for the AZ and NV surface water data, I don't think we have it, but Sam is checking. The questions about storage for hypochlorite should be in the AWWA protocol. Lisa

---

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 3:02 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

Lisa:
Please take a look at the comments/ revisions in the attached and let me know if you would like to have a call to discuss how to incorporate these changes.
Eric

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Monday, March 16, 2020 2:53 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Monday, March 16, 2020 2:49 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: EDITS - RE: Revised Perchlorate Briefing Documents
Importance: High

Hi Jennifer,

A few edits from Dave. Please review and confirm. In particular, please address the comment bubbles in the "Perchlorate Reductions" document. Please also review the write-up under #4 in the "Perchlorate Recommendations for PWS" document to confirm that it uses guidance type language, rather than authoritative, regulatory language. Due to formatting, yellow highlights (rather than redline) show changed text.

This is due tomorrow by noon, so please let me know as soon as the edits are incorporated.

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Friday, March 13, 2020 5:34 PM
To: Aguirre, Janita <Aguirre.Janita@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate Briefing Documents

Janita – your assistance on this is appreciated! Is it possible to provide these revised documents – updated per Dave's input?

Thank you
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, March 13, 2020 5:28 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Perchlorate Briefing Documents

Jennifer:
Attached please find a revised Perchlorate Briefing documents. We had submitted a previous versions of these document for OW review along with the Perchlorate Reductions and Recommendations Documents. We have updated these documents while awaiting further comments from OW. The revisions made to the documents are as follows

- The one pager – Decision for Perchlorate Final Regulatory Action – Has been updated in response to Dave's request to incorporate information about the timing of the release of the stipulation to NRDC regarding the consent decree. This document reflects OGC's input.
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- The Recommendations Document has been updated to reflect add a Document Number.

If OW has not yet reviewed the last versions provided we recommend sending these forward to replace the versions awaiting review. If there are comments on the previous versions we can incorporate those prior to sending them forward.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 10/27/2017 1:01:55 PM
To: Flowers, Lynn [Flowers.Lynn@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Bussard, David [Bussard.David@epa.gov]
Subject: RE: DRAFT FINAL MCLG Approach Charge 20171024.docx

Thanks Lynn – we'd like to wrap up the charge this week if possible. The OSA meeting went okay, they had a few questions about Dr. Pearce, although she was on the first panel. Also asked if we needed a toxicologist, but seemed satisfied with our skill mix.
Lisa

From: Flowers, Lynn
Sent: Friday, October 27, 2017 7:53 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Bussard, David <Bussard.David@epa.gov>
Subject: Re: DRAFT FINAL MCLG Approach Charge 20171024.docx

Sorry. We will have a comment on 13's new text. Will send ASAP. Hope your meeting with OSA went well.

Sent from my iPhone

On Oct 24, 2017, at 12:53 PM, Christ, Lisa <Christ.Lisa@epa.gov> wrote:

> All,
> The team has reviewed the comments received on the charge from: SBA, NASA, AWWA, DOD, NASA, AMWA and Intertox/PSG and made the attached revisions. Many of the comments were repeats of previous concerns – some already addressed. We meet with OSA this Thursday for final peer review panel selection and we can task the panel once the charge is final. Please send any comments/edits NLT Thursday COB. Let me know if you want to see the incoming comments…
> Thank you in advance
> Lisa
>
> ---
>
> **From:** Hafez, Ahmed
> **Sent:** Tuesday, October 24, 2017 10:57 AM
> **To:** Christ, Lisa <Christ.Lisa@epa.gov>
> **Cc:** Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>
> **Subject:** DRAFT FINAL MCLG Approach Charge 20171024.docx
>
> Hi Lisa,
>
> Please find the attached revised version of the Perchlorate charge. Based on the comments received, the revisions were minor and mostly clarifying in nature.
>
> Let me know if you have any questions or would like to discuss of the edits.
>
> Regards,
> Ahmed

Ahmed M. Hafez, Ph.D.
OW/OGWDW/SRMD/TAB | Office: WJC East 2227Q
hafez.ahmed@epa.gov | phone: 202.564.1944

"It is better to do things that you cannot explain, than to explain things that you cannot do."
--Nassim Taleb

<DRAFT FINAL MCLG Approach Charge 20171024.docx>

Message

From: Albert, Ryan [Albert.Ryan@epa.gov]
Sent: 6/16/2020 8:34:37 PM
To: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Lan, Alexis [lan.alexis@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Harmon, Molly [harmon.molly@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics
Attachments: DRAFT Interagency and Agency Tox Assessment for PFBS_May 2020_SRMD.docx; Response to Peer Review 2 Comments on PFBS Toxicity Assessment.docx

Hi Crystal,

For your review, please find SRRB comments on the ORD PFBS toxicity assessment. Big thanks to **Alex, Rajiv, Molly,** and **Erin** for reviewing, and to **Alex** for coordinating the review. Because of the endpoint chosen in this assessment is the same as perchlorate, Sam and Lisa may also choose to review, mindful they both have much higher priorities this week. Please note, we do have a major comment on how ORD conducted the evaluation provided from the perchlorate perspective (thank you Rajiv)!

Regarding timing, comments are due back to ORD by 6/30 but if we can get them to Greg Miller by 6/25, he will consolidate OW feedback into a single draft. We are sending to you now in the event that either Eric or either Yu-Ting or Jennifer are interested in seeing our comments or providing their own comments. Note the email exchange below where Jennifer flagged the perchlorate issue to Betsy (with a cc to Eric). Comments below:

Major comment

- Please see comment on page ix regarding the critical effect for derivation of the draft subchronic and chronic RfD.

Minor comments

- There's a description of UCMR3 PFBS occurrence on page 2 of the draft assessment. SRRB looked into the data and can verify that their statements surrounding states reporting > MRL as well as population served (based on a 2020 pull) are both accurate.
- No studies were identified that evaluated the association between PFBS exposure and potential cancer outcomes. While the Agency did review studies submitted by 3M as part of TSCA premanufacturing notices, the assessment ultimately concluded "inadequate evidence to assess carcinogenic potential."
- Minor wording changes are reflected in tracked changes throughout the document.

Thank you,
Ryan

From: Lan, Alexis
Sent: Tuesday, June 02, 2020 3:53 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Albert, Ryan <Albert.Ryan@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics

Good afternoon Lisa and Ryan,

Thank you both for chatting earlier. Please see the message from Greg Miller below. I suspect that Crystal, Eric and Jennifer will also want to review and provide feedback. To facilitate those reviews in time, here is what I propose in terms of next steps:

- Provide staff-level (SRRB/TAB) comments to Lisa and Ryan by **COB Tuesday 6/9**
- Lisa and Ryan to review and provide comments to Crystal and/or Eric by **Tuesday 6/16**
- Transmit consolidated SRMD comments to Jennifer by **Tuesday 6/23**

I'll be happy to coordinate and consolidate comments during this process. Please let me know if you have any questions or concerns, and thank you in advance for your time on this review.

All the best,

Alex Lan, MPH
Physical Scientist
Office of Ground Water and Drinking Water
Standards and Risk Management Division
U.S. Environmental Protection Agency
Washington, D.C.
Lan.Alexis@epa.gov
(Desk) 202.564.0841
(Mobile) 703.303.7791

From: Miller, Gregory <Miller.Gregory@epa.gov>
Sent: Tuesday, June 02, 2020 2:45 PM
To: Lan, Alexis <lan.alexis@epa.gov>
Cc: Strong, Jamie <Strong.Jamie@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics

Hi Alex,
Attached you will find the PFBS Toxicity Assessment that is being shared for internal EPA review through the usual IRIS process. I'm sharing these documents with you as the point of contact for OGWDW. Jennifer McLain has flagged the thyroid (email below) as an area of concern given the perchlorate NPDWS rule withdrawal currently under review at OMB. Please coordinate your response with the perchlorate team in OGWDW (Sam, Rajiv, Lisa) as you draft your comments. Comments are due to ORD by 6/30, but if you could have your comments to me by 6/25, I will combine the OST and OGWDW comments into one document as was requested.

Thanks!

Greg Miller, Senior Environmental Health Scientist
Team Lead, Human Health Risk Assessment Branch
Office of Science and Technology, Health and Ecological Criteria Division
US Environmental Protection Agency, Office of Water
1200 Pennsylvania Ave, NW (MC 4304T)
Washington, DC 20460

phone: (202) 566-2310

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Monday, June 01, 2020 11:31 AM
To: Behl, Betsy <Behl.Betsy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: PFBS assessment

Betsy – you may already be doing this but I wanted to make sure we are connected to ORD as they respond to their peer review comment: Need for additional clarifying language on the physiology and function of thyroid hormones during

pregnancy and further description of the clinical condition "hypothyroxinemia". I'm reviewing the perchlorate response to comment document now and just want to make sure we are being consistent.

Thanks
Jennifer

From: Jones, Samantha <Jones.Samantha@epa.gov>
Sent: Monday, June 1, 2020 5:34 PM
To: Cassidy, Meghan <Cassidy.Meghan@epa.gov>; Olsen, Marian <Olsen.Marian@epa.gov>; Rogers, Rick <rogers.rick@epa.gov>; Gehlhaus, Martin <Gehlhaus.Martin@epa.gov>; Allenbach, Becky <Allenbach.Becky@epa.gov>; Pollard, Solomon <Pollard.Solomon@epa.gov>; Adams, Glenn <Adams.Glenn@epa.gov>; Harris, Kimberly <harris.kimberly@epa.gov>; Mangino, Mario <mangino.mario@epa.gov>; Morton, Michael <Morton.Michael@epa.gov>; Milburn, Anna <Milburn.Anna@epa.gov>; Wooster-Brown, Catherine <Wooster-Brown.Catherine@epa.gov>; Schumacher, Kelly <Schumacher.Kelly@epa.gov>; Bahrman, Sarah <Bahrman.Sarah@epa.gov>; Benson, Bob <Benson.Bob@epa.gov>; Small, Matthew <Small.Matthew@epa.gov>; Stralka, Daniel <Stralka.Daniel@epa.gov>; Allen, Elizabeth <allen.elizabeth@epa.gov>; Anderson-Carnahan, Linda <Anderson-Carnahan.Linda@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>; Barone, Stan <Barone.Stan@epa.gov>; Hamernik, Karen <Hamernik.Karen@epa.gov>; Raffaele, Kathleen <raffaele.kathleen@epa.gov>; Murphy, Deirdre <Murphy.Deirdre@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Hoyer, Marion <hoyer.marion@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>; Dzubow, Rebecca <Dzubow.Rebecca@epa.gov>; Lloyd, Christine <Lloyd.Christine@epa.gov>
Cc: Owens, Beth <Owens.Beth@epa.gov>; Lambert, Jason <Lambert.Jason@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>
Subject: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics

Hello all,

You are receiving this email because you have been identified as your office's point of contact for review of toxicity assessments in general and/or as the PFAS point of contact. If this has reached you by mistake and there is another individual that should be the point person, please let me know as soon as you can.

This email is to initiate the internal agency review of the revised PFBS toxicity assessment. Shortly, you will be granted access to the SharePoint site (see link below) so that you will be able to obtain the PFBS draft toxicity assessment as well as the Response to peer review comments document. Please feel free to circulate the materials within your respective office, we just ask that as the points of contact, that you compile and upload one set of comments from your respective office. We request that you post comments to the SharePoint site by **COB Tuesday, June 30th**.

https://usepa.sharepoint.com/sites/ORD_Work/pfas_toxval_internal_review/SitePages/Home.aspx

We appreciate your feedback. Please let me know if there are any questions.

Thank you!
Samantha

Samantha J. Jones, PhD
Associate Director, Center for Public Health and Environmental Assessment (CPHEA)
National Program Director, Health and Environmental Risk Assessment (HERA) Research Program
Office of Research and Development (ORD)
US Environmental Protection Agency (EPA)
RRB 71210, Washington, DC
(o) 202-564-6794; (m) 703-943-7990

Message

From: Tiago, Joseph [Tiago.Joseph@epa.gov]
Sent: 3/16/2020 6:52:31 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: McLain, Jennifer L. [McLain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents
Attachments: Perchlorate Recommendations for PWS_03.16.2020.docx; Perchlorate Reductions_03.16.2020.docx; Decision for Perchlorate Final Regulatory Action_3-13-20_revisedOWIO.docx

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Sent: Monday, March 16, 2020 2:49 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: EDITS - RE: Revised Perchlorate Briefing Documents
Importance: High

Hi Jennifer,

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This is due tomorrow by noon, so please let me know as soon as the edits are incorporated.

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Friday, March 13, 2020 5:34 PM
To: Aguirre, Janita <Aguirre.Janita@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate Briefing Documents

Janita – your assistance on this is appreciated! Is it possible to provide these revised documents – updated per Dave's input?

Thank you
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, March 13, 2020 5:28 PM

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Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
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Jennifer:
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Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 6/3/2020 6:00:21 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: FOR REVIEW: draft perchlorate response to comment document
Attachments: Consolidated Perchlorate Draft Comment Response Document.jlm.5-30-2020.docx

Lisa and team – thank you for all your work on these responses to comments. They are very well written. You will see that I added a number of cross-references involving the summary responses. Other than that, there are a few issues flagged for your consideration. Please let me know if you want to discuss any of these.

Jennifer

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, May 19, 2020 6:41 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FOR REVIEW: draft perchlorate response to comment document

DRAFT/DELIBERATIVE
Hello Jennifer,
Attached for your is the draft perchlorate response to comment document. Please let us know if you have questions or concerns.
Thanks,
Lisa

Message

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Sent: 10/24/2017 4:53:35 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Bussard, David [Bussard.David@epa.gov]
CC: Behl, Betsy [Behl.Betsy@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: DRAFT FINAL MCLG Approach Charge 20171024.docx
Attachments: DRAFT FINAL MCLG Approach Charge 20171024.docx

All,
The team has reviewed the comments received on the charge from: SBA, NASA, AWWA, DOD, NASA, AMWA and Intertox/PSG and made the attached revisions. Many of the comments were repeats of previous concerns – some already addressed. We meet with OSA this Thursday for final peer review panel selection and we can task the panel once the charge is final. Please send any comments/edits NLT Thursday COB. Let me know if you want to see the incoming comments…
Thank you in advance
Lisa

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Sent: Tuesday, October 24, 2017 10:57 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>
Subject: DRAFT FINAL MCLG Approach Charge 20171024.docx

Hi Lisa,

Please find the attached revised version of the Perchlorate charge. Based on the comments received, the revisions were minor and mostly clarifying in nature.

Let me know if you have any questions or would like to discuss of the edits.

Regards,
Ahmed

Ahmed M. Hafez, Ph.D.
OW/OGWDW/SRMD/TAB | Office: WJC East 2227Q
hafez.ahmed@epa.gov | phone: 202.564.1944

"It is better to do things that you cannot explain, than to explain things that you cannot do."
--Nassim Taleb

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 5/17/2020 9:45:02 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: Notice of Final Action on Perchlorate
Attachments: Perchlorate Action Memo 5-15-20.docx

Thanks all! Just a few comments in the attached.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 15, 2020 5:03 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: Notice of Final Action on Perchlorate

Jennifer

Attached for your approval and transmittal to the Office of Water for their approval and transmittal to the Office Policy for initiation of interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate." Also attached for your review are a draft transmittal memo from you to the Assistant Administrator of Water, a draft Action Memorandum and a track changes version of the FR notice that denotes the changes made as a result of Final Agency Review.

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

I recommend that you approve and transmit the attached notice to the Office of Water for their review, approval and transmission to the Office of Policy to initiate interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 5/6/2020 7:51:23 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FOR REVIEW: draft perchlorate action and transmittal memos
Attachments: Perchlorate Action Memo 4-13-2020 v1.docx; Transmittal Memo EB to JM 4-13-20.v1.docx; Transmittal Memo JM to DR 4-13-20 v1.docx

DRAFT DELIVERABLE
Hi Eric,
For you review are the draft memos to accompany the perchlorate final action. Please let us know if you have question, concerns or need more information.
Thanks,
Lisa

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Regulatory Determination on Perchlorate

FROM: Eric G. Burneson, Director
Standards and Risk Management Division
Office of Ground Water and Drinking Water

TO: Jennifer L. McLain, Director
Office of Ground Water and Drinking Water

Attached for your approval and transmittal to the Assistant Administrator for the Office of Water is a *Federal Register* notice titled: Notice of Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Regulatory Determination on Perchlorate.

On June 26, 2019 (84 FR 30524), the EPA published a proposed National Primary Drinking Water Regulation (NPDWR) for perchlorate and requested public comment on multiple alternative regulatory actions, including the alternative of withdrawing the 2011 regulatory determination for perchlorate. The Agency received approximately 1,500 comments on the proposed rule. In consideration of public comments and based on the best available human health and occurrence information, the Agency is withdrawing the 2011 regulatory determination and is making a final determination not to regulate perchlorate by publication of this *Federal Register* notice.

In determining whether to regulate a contaminant, the EPA must follow the criteria mandated by the 1996 Safe Drinking Water Act (SDWA) Amendments. Specifically, in order to issue a MCLG and NPDWR for perchlorate, the EPA must determine that perchlorate "may have an adverse effect on the health of persons," that perchlorate occurs at "a frequency and at levels of public health concern" in public water systems, and that regulation of perchlorate in drinking water systems "presents a meaningful opportunity for health risk reductions for persons served by public water systems." SDWA 1412(b)(1)(A). Based on the EPA's new analysis and after careful review and consideration of public comments on the June 2019 proposal, the Agency is withdrawing its 2011 determination and is now making a determination not to regulate perchlorate. While the EPA has found that perchlorate may have an adverse effect on human health, the EPA has determined that perchlorate does not occur in public water systems at a frequency and at levels of public health concern and regulation of perchlorate does not present a meaningful opportunity to reduce health risks for persons served by public water systems. This conclusion is based on the best available peer reviewed science and data collected in accordance with accepted methods on perchlorate health effects and occurrence. Accordingly, the EPA will not issue a NPDWR for perchlorate.

The EPA maintains the authority to re-list perchlorate on the Contaminant Candidate List (CCL) and proceed with regulating perchlorate in the future if occurrence or risk information changes to warrant this. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the affected system and state, or issuing a health advisory under the SDWA Section 1412(b)(1)(F), as appropriate. In addition, the EPA can also address the limited instances of perchlorate occurrence by working with the states and health assessment authorities under SDWA Section 1431, as appropriate.

I recommend that you approve and transmit the attached notice to the Assistant Administrator for the Office of Water for review. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachment

Federal Register Notice

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Regulatory Determination on Perchlorate

FROM: Jennifer L. McLain, Director
Office of Ground Water and Drinking Water

TO: David P. Ross
Assistant Administrator, Office of Water

Attached for your approval and transmittal to the Office of the Administrator is a *Federal Register* notice titled: Notice of Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Regulatory Determination on Perchlorate.

On June 26, 2019 (84 FR 30524), the EPA published a proposed National Primary Drinking Water Regulation (NPDWR) for perchlorate and requested public comment on multiple alternative regulatory actions, including the alternative of withdrawing the 2011 regulatory determination for perchlorate. The Agency received approximately 1,500 comments on the proposed rule. In consideration of public comments and based on the best available human health and occurrence information, the Agency is withdrawing the 2011 regulatory determination and is making a final determination not to regulate perchlorate by publication of this *Federal Register* notice.

In determining whether to regulate a contaminant, the EPA must follow the criteria mandated by the 1996 Safe Drinking Water Act (SDWA) Amendments. Specifically, in order to issue a MCLG and NPDWR for perchlorate, the EPA must determine that perchlorate "may have an adverse effect on the health of persons," that perchlorate occurs at "a frequency and at levels of public health concern" in public water systems, and that regulation of perchlorate in drinking water systems "presents a meaningful opportunity for health risk reductions for persons served by public water systems." SDWA 1412(b)(1)(A). Based on the EPA's new analysis and after careful review and consideration of public comments on the June 2019 proposal, the Agency is withdrawing its 2011 determination and is now making a determination not to regulate perchlorate. While the EPA has found that perchlorate may have an adverse effect on human health, the EPA has determined that perchlorate does not occur in public water systems at a frequency and at levels of public health concern and regulation of perchlorate does not present a meaningful opportunity to reduce health risks for persons served by public water systems. This conclusion is based on the best available peer reviewed science and data collected in accordance with accepted methods on perchlorate health effects and occurrence. Accordingly, the EPA will not issue a NPDWR for perchlorate.

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this. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the affected system and state, or issuing a health advisory under the SDWA Section 1412(b)(1)(F), as appropriate. In addition, the EPA can also address the limited instances of perchlorate occurrence by working with the states and health assessment authorities under SDWA Section 1431, as appropriate.

I recommend that you approve and transmit the attached notice to the Office of the Administrator for review. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachment

Federal Register Notice

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 3/17/2020 1:56:30 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents
Attachments: Perchlorate Reductions_03.17.2020 CleanV.docx; Perchlorate Recommendations for PWS_03.17.2020.CleanV.docx

Hi Eric,

Here are the clean versions of both documents. I did not see any suggested edits from Jennifer or Joe, let me know if there is any additional edits needed.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, March 17, 2020 9:30 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Lisa: I have made additional edits to the documents attached to further expand the introduction to the Reductions Document and to address the POU text by describing the option as a Point of Use or Point of Entry Treatment option. Can you/Sam prepare clean versions of these documents so that we are ready for the 10:00 deadline.

Joe, Yu Ting and Jennifer
I am assuming Dave needs to see the mark ups to verify the edits so I am copying you in case you want to review while we are preparing clean versions.
Eric

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, March 17, 2020 8:16 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric, please see the revised document attached. I noticed we were missing references we added on 2/28 so I put those back in the reductions document. I do not agree with a edit on page 2 (highlighted blue) stating POU protects the whole home. Let us know if you'd like additional changes.

Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 4:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Thanks. Can I get a revised by 8:30 am tomorrow morning?

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, March 16, 2020 3:42 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric,
I think they are mostly straight forward. If I recall we were asked previously for underlying data for the AZ and NV surface water data, I don't think we have it, but Sam is checking. The questions about storage for hypochlorite should be in the AWWA protocol. Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 3:02 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

Lisa:
Please take a look at the comments/ revisions in the attached and let me know if you would like to have a call to discuss how to incorporate these changes.
Eric

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Monday, March 16, 2020 2:53 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Monday, March 16, 2020 2:49 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: EDITS - RE: Revised Perchlorate Briefing Documents
Importance: High

Hi Jennifer,

A few edits from Dave. Please review and confirm. In particular, please address the comment bubbles in the "Perchlorate Reductions" document. Please also review the write-up under #4 in the "Perchlorate

Recommendations for PWS" document to confirm that it uses guidance type language, rather than authoritative, regulatory language. Due to formatting, yellow highlights (rather than redline) show changed text.

This is due tomorrow by noon, so please let me know as soon as the edits are incorporated.

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Friday, March 13, 2020 5:34 PM
To: Aguirre, Janita <Aguirre.Janita@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate Briefing Documents

Janita – your assistance on this is appreciated! Is it possible to provide these revised documents – updated per Dave's input?

Thank you
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, March 13, 2020 5:28 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Perchlorate Briefing Documents

Jennifer:
Attached please find a revised Perchlorate Briefing documents. We had submitted a previous versions of these document for OW review along with the Perchlorate Reductions and Recommendations Documents. We have updated these documents while awaiting further comments from OW. The revisions made to the documents are as follows

- The one pager – Decision for Perchlorate Final Regulatory Action – Has been updated in response to Dave's request to incorporate information about the timing of the release of the stipulation to NRDC regarding the consent decree. This document reflects OGC's input.
- The Reductions Document – has been updated to reflect the information we received from the States of Maryland and Ohio regarding the status of the system that previously detected perchlorate at levels greater than 18ppb. We have also added a document number.
- The Recommendations Document has been updated to reflect add a Document Number.

If OW has not yet reviewed the last versions provided we recommend sending these forward to replace the versions awaiting review. If there are comments on the previous versions we can incorporate those prior to sending them forward.

Eric Burneson, P.E.

Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 5/6/2020 3:42:23 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: quick turn around
Attachments: OCHP comments attached - RE: ADP workgroup review - perchlorate DW reg; Reminder: Request for review - Draft Perchlorate Rule Proposal ; RE: ADP workgroup review - perchlorate DW reg

Hi Eric,

Attached are the emails that I sent out requesting comment of the draft documents for perchlorate. Also attached you will see OCHP input/response.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, May 06, 2020 10:21 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: quick turn around
Importance: High

Hi Sam,
I need your help to respond to OCHP. What interactions have we had with the workgroup and in particular with OCHP on perchlorate. There are questions about how 'FAR" was conducted for the proposal. Please let me know about emails, etc.
Thanks!
Lisa

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Message

From: Louie, Nica [Louie.Nica@epa.gov]
Sent: 2/14/2019 10:03:46 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Firestone, Michael [Firestone.Michael@epa.gov]; Foos, Brenda [Foos.Brenda@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: OCHP comments attached - RE: ADP workgroup review - perchlorate DW reg
Attachments: OCHP comments 2019 perchlorate rule_February 14 2019.docx

Hi Sam –

Thank you for the opportunity to comment and please let me know if you have any questions.

- nica

Nica Louie
Regulatory Support and Science Policy Division
U.S. EPA Office of Children's Health Protection
1300 Pennsylvania Ave., NW,
Washington, D.C. 20004
202-564-7633

From: Hernandez-Quinones, Samuel
Sent: Wednesday, February 06, 2019 9:52 AM
To: Louie, Nica <Louie.Nica@epa.gov>
Cc: Firestone, Michael <Firestone.Michael@epa.gov>; Foos, Brenda <Foos.Brenda@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: ADP workgroup review - perchlorate DW reg

Preliminary draft for internal EPA review

Hi Nica,

Attached for your review is the Draft Perchlorate Rule Proposal (Preamble and Regulatory Text). I am requesting that you provide your questions and or comments on the draft document to me by COB 2/15/2019. In order to keep with the consent decree deadline, we need to complete this step of the process within two weeks, if there are any issues that require technical discussions please let me know so that we can arrange any necessary working meeting.

Also attached you will find the draft version of the technical support documents that were used as the basis for the Perchlorate proposal. Since these are very lengthy documents we are not requesting that you submit input and/or comments on those within the two- week time frame.

- Economic Analysis
- MCLG Derivation Document

- Treatment Technologies & Costs Document
- Occurrence & Monitoring Report
- MCLG Approaches Document
- Best Available Technologies Document

Please know that that we expect a close hold on these documents, so I would appreciate if these are not circulated around. Let me know if you have any questions.

Thanks

Sam

==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Louie, Nica
Sent: Tuesday, February 05, 2019 8:18 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Firestone, Michael <Firestone.Michael@epa.gov>; Foos, Brenda <Foos.Brenda@epa.gov>
Subject: ADP workgroup review - perchlorate DW reg

Hi Sam –

Could you please let me know regarding the status of the review and when OCHP can expect to receive copies of the proposed rule and supporting documents for review/comment?

Thank you – and I was thinking of you during the shutdown and how it would impact you.

- nica

Nica Louie
Program Officer
EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers
National Center for Environmental Research
U.S. Environmental Protection Agency

On Detail at
Regulatory Support and Science Policy Division
U.S. EPA Office of Children's Health Protection
1300 Pennsylvania Ave., NW,
Washington, D.C. 20004
202-564-7633

February 14, 2019

MEMORANDUM

SUBJECT: Office of Children's Health Protection (OCHP) input for the Draft National Primary Drinking Water Regulations: Proposed Perchlorate Rule

FROM: Nica Louie, Perchlorate Workgroup Member, OCHP, Regulatory Support and Science Policy Division (RSSPD)

TO: Samuel Hernández Quiñones, Chair Perchlorate Workgroup, Office of Water

The Office of Children's Health Protection (OCHP) appreciates the opportunity to comment on the Draft National Primary Drinking Water Regulations: Proposed Perchlorate Rule. As you are aware, the last meeting of the perchlorate workgroup was in August 2018, and much progress has been made since then. We regret that the workgroup has not been more involved and that this is our first opportunity provide children's environmental health input as the rule is being finalized. As you will appreciate, a tremendous amount of information has been provided for review over a short period of time and we have done our best to address children's environmental health concerns and provide comments in the limited timeframe. Key OCHP concerns and recommendations have been summarized below.

OVERALL: OCHP is highly concerned with the proposed Maximum Contaminant Level (MCL) and Maximum Contaminant Level Goal (MCLG) for perchlorate of 56 ug/L, which are much higher than previous efforts by EPA and others.

- **A two percent intelligence quotient (IQ) loss from exposure to a single contaminant is a significant health problem for children. While selecting a 0.5 percent IQ loss would be better, OCHP strongly recommends an even lower decrease in IQ as the basis for calculating the perchlorate MCLG.**

  We believe that it is imperative to lay a more inclusive foundation to address the disproportionate variations in sensitivity for the fetus, newborns, infants, children, lactating women and thyroid compromised adults. [FR Page 33]

- **While OCHP concurs that the first trimester is one of the most sensitive developmental life stages, we strongly recommend the inclusion of other sensitive life stages in the proposed quantitative approach. The first trimester is not inclusive of the continuum of potentially sensitive life stages.**

  Developmental toxicology is complex and while there have been significant advances in the ability to model adverse health effects from environmental contaminants, the process is still burdened with significant uncertainties. It is therefore critical to extend the model to include all stages of pregnancy, newborns, infants (especially formula-fed), and children using life stage-specific body weight and exposure information. We note that individuals are rarely exposed for one single life stage and each life stage has unique sensitivities. For example, many infants receive inadequate levels of iodine in their diet as seen in a study of nursing mothers in Boston. The study found that 47 percent of breast milk samples contained iodine levels below those recommended by the

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Institute of Medicine (CalEPA 2015). Another important characteristic is that infants have a low store of thyroid hormone (less than one day's worth, compared to several weeks' worth in adults) (CalEPA 2015). Additionally, the 2017 BBDR model peer review recommended extending the model to include early pregnancy (and not replace).

We request that all future efforts include all lifestages. We understand that time and resources are limited and recognize the need to focus on the first trimester for the draft FR. We also request transparency about the time limitation when describing the reliance on the first trimester and recommend addition of the following text as a footnote on page 20 of the FR.

> "A full analysis would include all stages of pregnancy, newborns, infants (especially formula-fed), and children using life stage-specific body weight and exposure information. In consideration of limited time and resources, the proposed MCL/MCLG have been calculated for one of the most sensitive populations."

- While OCHP acknowledges the inclusion of a 3 fold UF, we believe that this does not sufficiently address the uncertainties associated with the perchlorate dose response modeling, as well as variations in sensitivity for the fetus during the second and third trimester, newborns, infants, children, lactating women and thyroid compromised adults. **OCHP highly recommends a much higher UF given that neurodevelopmental disorders affect one of every six 3-17-year-old children in the United States.** [FR Page 34] (Landrigan and Etzel, 2014)

  Additional uncertainties

  - The current analysis underestimates the impact of perchlorate by not accounting for goitrogens that compound the impact of perchlorate. Examples include thiocyanate from smoking and nitrates which are extensively used in food and are present in drinking water.
  - Another concern is the lack of actual data for model calibration/validation to estimate the degree of hormone perturbation from perchlorate interference with iodine uptake[1]. There are also conflicting findings in epidemiology and human exposure trials. For example, several epidemiological studies suggest greater effect than the BBDR prediction while higher dose human studies do not show hormone effect.

- Recommend that OW reconsider using 15th-20th percentile of iodine intake because this results in exclusion of a large portion of the population, especially since there is substantial variability and day to day variations in urinary iodine concentration which can result in inaccurate estimates of iodine intake. [FR Page 25]

[1] Page 3-1 and 3-14 of the Proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water Volume I, November 2018

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- OCHP recommends using the 99th or 95th percentile distributions for drinking water and perchlorate consumption because 10% of the population is a large number of individuals excluded from the analysis when the 90th percentile is used. [FR Pages 38-40]

Specific Recommendations

In accordance with Executive Order 12866 which encourages federal agencies to write rules in plain language and for clarity, OCHP encourages the following minor changes:

- We see that the term "offspring" has been used many times in the document when referring to children. Although this is not technically incorrect, the term "offspring" is typically used in reference to animal models and we request that you replace this word with "child" or "children" when that is the subject of the text, throughout the document.

- Recommend replacing neonate with newborn. Although technically correct, the term newborn is more accessible as plain language.

- Units need to be presented in a consistent fashion. The report presents the proposed MCLG in mg/L with ug/L in parenthesis and then switches the order for the previously recommended RFD on page 10 and onwards. This method is both inconsistent and confusing.

References

California Environmental Protection Agency (CalEPA). (2015). Public Health Goal for Perchlorate in Drinking Water

Landrigan P and Etzel R, New Frontiers in Children's Environmental Health, in Textbook of Children's Environmental Health, P. Landrigan and R. Etzel, Editors. 2014, Oxford University Press: New York, NY

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Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/6/2019 2:51:53 PM
To: Louie, Nica [Louie.Nica@epa.gov]
CC: Firestone, Michael [Firestone.Michael@epa.gov]; Foos, Brenda [Foos.Brenda@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: ADP workgroup review - perchlorate DW reg
Attachments: Version-Control Perchlorate Rule FRN 2-4-19.docx; 181129_DRAFT MCLG TSD.DOCX; Draft Perchlorate HRRCA 2019-02-03.docx; PerchlorateOccMonitoringReport_Updated 2-1-19.docx; Perchlorate T&C November 2018.docx; Perchlorate BAT and SSCT November 2018.docx; WA459_T4_Vol1 Main Report_181113.docx

Preliminary draft for internal EPA review

Hi Nica,

Attached for your review is the Draft Perchlorate Rule Proposal (Preamble and Regulatory Text). I am requesting that you provide your questions and or comments on the draft document to me by COB 2/15/2019. In order to keep with the consent decree deadline, we need to complete this step of the process within two weeks, if there are any issues that require technical discussions please let me know so that we can arrange any necessary working meeting.

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- MCLG Derivation Document
- Treatment Technologies & Costs Document
- Occurrence & Monitoring Report
- MCLG Approaches Document
- Best Available Technologies Document

Please know that that we expect a close hold on these documents, so I would appreciate if these are not circulated around. Let me know if you have any questions.

Thanks

Sam

==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

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Sent: Tuesday, February 05, 2019 8:18 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Firestone, Michael <Firestone.Michael@epa.gov>; Foos, Brenda <Foos.Brenda@epa.gov>
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Thank you – and I was thinking of you during the shutdown and how it would impact you.

- nica

Nica Louie
Program Officer
EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers
National Center for Environmental Research
U.S. Environmental Protection Agency

On Detail at
Regulatory Support and Science Policy Division
U.S. EPA Office of Children's Health Protection
1300 Pennsylvania Ave., NW,
Washington, D.C. 20004
202-564-7633

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/13/2019 6:07:29 PM
To: Johnson, Ann [Johnson.Ann@epa.gov]; Dockins, Chris [Dockins.Chris@epa.gov]; Shao, Nicole [Shao.Nicole@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Foster, Stiven [Foster.Stiven@epa.gov]; Kyprianou, Rose [Kyprianou.Rose@epa.gov]; Miller, Wynne [Miller.Wynne@epa.gov]; Raffaele, Kathleen [raffaele.kathleen@epa.gov]; Louie, Nica [Louie.Nica@epa.gov]; Foos, Brenda [Foos.Brenda@epa.gov]; Firestone, Michael [Firestone.Michael@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: Reminder: Request for review - Draft Perchlorate Rule Proposal

Hi, this serves as a friendly reminder that your comments on the Draft Perchlorate Rule proposal are due no later than **COB Friday 2/15/19**.

Please let me know if you have any questions.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 3/17/2020 1:37:37 PM
To: Wadlington, Christina [Wadlington.Christina@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents
Attachments: Perchlorate Recommendations for PWS_03.17.2020.Changes.docx; Perchlorate Reductions_03.17.2020RLSO.docx

Christina – asap would you please let us know if you have any concerns with the changes in the perchlorate recommendations document?

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, March 17, 2020 9:34 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

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From: Burneson, Eric
Sent: Tuesday, March 17, 2020 9:30 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Joe Tiago (Tiago.Joseph@epa.gov) <Tiago.Joseph@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Lisa: I have made additional edits to the documents attached to further expand the introduction to the Reductions Document and to address the POU text by describing the option as a Point of Use or Point of Entry Treatment option. Can you/Sam prepare clean versions of these documents so that we are ready for the 10:00 deadline.

Joe, Yu Ting and Jennifer
I am assuming Dave needs to see the mark ups to verify the edits so I am copying you in case you want to review while we are preparing clean versions.
Eric

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, March 17, 2020 8:16 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric, please see the revised document attached. I noticed we were missing references we added on 2/28 so I put those back in the reductions document. I do not agree with a edit on page 2 (highlighted blue) stating POU protects the whole home. Let us know if you'd like additional changes.

Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 4:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Thanks. Can I get a revised by 8:30 am tomorrow morning?

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, March 16, 2020 3:42 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric,
I think they are mostly straight forward. If I recall we were asked previously for underlying data for the AZ and NV surface water data, I don't think we have it, but Sam is checking. The questions about storage for hypochlorite should be in the AWWA protocol. Lisa

---

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 3:02 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

Lisa:
Please take a look at the comments/ revisions in the attached and let me know if you would like to have a call to discuss how to incorporate these changes.
Eric

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Monday, March 16, 2020 2:53 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

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From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Monday, March 16, 2020 2:49 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: EDITS - RE: Revised Perchlorate Briefing Documents
Importance: High

Hi Jennifer,

A few edits from Dave. Please review and confirm. In particular, please address the comment bubbles in the "Perchlorate Reductions" document. Please also review the write-up under #4 in the "Perchlorate Recommendations for PWS" document to confirm that it uses guidance type language, rather than authoritative, regulatory language. Due to formatting, yellow highlights (rather than redline) show changed text.

This is due tomorrow by noon, so please let me know as soon as the edits are incorporated.

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Friday, March 13, 2020 5:34 PM
To: Aguirre, Janita <Aguirre.Janita@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate Briefing Documents

Janita – your assistance on this is appreciated! Is it possible to provide these revised documents – updated per Dave's input?

Thank you
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, March 13, 2020 5:28 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Perchlorate Briefing Documents

Jennifer:
Attached please find a revised Perchlorate Briefing documents. We had submitted a previous versions of these document for OW review along with the Perchlorate Reductions and Recommendations Documents. We have updated these documents while awaiting further comments from OW. The revisions made to the documents are as follows

- The one pager – Decision for Perchlorate Final Regulatory Action – Has been updated in response to Dave's request to incorporate information about the timing of the release of the stipulation to NRDC regarding the consent decree. This document reflects OGC's input.
- The Reductions Document – has been updated to reflect the information we received from the States of Maryland and Ohio regarding the status of the system that previously detected perchlorate at levels greater than 18ppb. We have also added a document number.
- The Recommendations Document has been updated to reflect add a Document Number.

If OW has not yet reviewed the last versions provided we recommend sending these forward to replace the versions awaiting review. If there are comments on the previous versions we can incorporate those prior to sending them forward.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 10/4/2017 4:09:05 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension
Attachments: ACC Response Letter.docx; AWWA Response Letter.docx; Chlorine Institute Response Letter.docx; PSG Response Letter.docx

Hi Lisa,

Attached are the revised letters for your review. I placed Peter in the signature block for all letters, also I added language to indicate that Peter was responding to the letters sent to Shapiro (PSG & AWWA).

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa
Sent: Wednesday, October 04, 2017 11:35 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

Hi Sam,
FYI – Peter would like to sign the letters – please see highlighted note below. Please revise the letters for Peter's signature and send me the e-copies for review. I'm out this afternoon, back tomorrow.

Lisa

From: Tiago, Joseph
Sent: Wednesday, October 04, 2017 11:32 AM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

Hi Crystal,

I checked with Peter:

- Eric to make a phone contact to the organizations that submitted the request to Mike and tell them that a FRN will come out soon with an extension of the public comment period. – This can be done as soon as today since Mike signed the package.

- SRMD to draft a formal letter response to those entities for Peter to sign on behalf of Mike. – The letter should state that Mike asked Peter to respond. Let coordinate on this.

Thanks,

Joe.

From: Rodgers-Jenkins, Crystal
Sent: Wednesday, October 4, 2017 10:08 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

On Sept 29th, Peter wrote to Mike (see email chain below)

First, we'll appreciate your input on whether we need to seek input from the AO on this approach as well. If we are good to move forward, we would communicate with the organizations that submitted the requests informally, then we'll need to draft formal response letters and quickly put together the FR notices that will be needed to modify the public comment periods. We'll certainly need your help to get these approved quickly.

I am checking in so that we can all be clear on who will informally communicate to the organizations about our response to their request. I am guessing the calls would need to happen this week. My understanding is that the FR notice went upstairs this morning and we expect the FR to be published next week.

I've asked Lisa to draft a few talking points in case Peter is planning to make the calls. We are fine with making the calls if Peter wishes to delegate to SRMD management.

Please let us know.

Take care,
Crystal

From: Burneson, Eric
Sent: Tuesday, October 03, 2017 8:06 AM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Fwd: Perchlorate public comment period extension requests

Crystal
I have not yet reviewed this notice. Can you please review and move forward as soon as Lisa gets this to you?

Thanks

Sent from my iPhone

Begin forwarded message:

> **From:** "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Date:** October 2, 2017 at 1:43:46 PM EDT
> **To:** "Flaharty, Stephanie" <Flaharty.Stephanie@epa.gov>
> **Cc:** "Christ, Lisa" <Christ.Lisa@epa.gov>, "Huff, Lisa" <Huff.Lisa@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>, "Tiago, Joseph" <Tiago.Joseph@epa.gov>, "Tricas, Marisa" <tricas.marisa@epa.gov>
> **Subject: Re: Perchlorate public comment period extension requests**
>
> Great. I will Lee know we are aiming for his review on Thursday.
>
> Jennifer
>
> On Oct 2, 2017, at 11:50 AM, Flaharty, Stephanie <Flaharty.Stephanie@epa.gov> wrote:
>
> > Thanks Lisa !
> >
> > ---
> >
> > **From:** Christ, Lisa
> > **Sent:** Monday, October 02, 2017 12:49 PM
> > **To:** Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
> > **Cc:** Huff, Lisa <Huff.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
> > **Subject:** RE: Perchlorate public comment period extension requests
> >
> > Hi Stephanie,
> > Sam already drafted a notice that I reviewed – he's getting OGC concurrence. He also drafted transmittal memos. WE should be circulating them for review soon.
> > Lisa
> >
> > ---
> >
> > **From:** Flaharty, Stephanie
> > **Sent:** Monday, October 02, 2017 12:40 PM
> > **To:** Mclain, Jennifer <Mclain.Jennifer@epa.gov>
> > **Cc:** Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
> > **Subject:** FW: Perchlorate public comment period extension requests
> >
> > Jennifer,
> >
> > I have an FR template that we used for the last extension so I can draft the new notice. **Please let me know how much time we're are granting for the extension.**
> >
> > **Peter can sign the notice but we need to clear FRNs through OP prior to signature**. Mike is out all week and Lee is in the office this Thursday and Friday. He is on travel all next week so this Thursday is our opportunity to have him send an email to clear the FRN through OP and higher. I'll need to end OW the draft FRN and action

information sheet by Thursday morning and Macara will request that Lee clear it before he goes on travel next week.

Please let me know if you all can work with the timing.

Thanks,
Steph

Begin forwarded message:

> **From:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
> **Date:** October 2, 2017 at 10:51:50 AM EDT
> **To:** "Evalenko, Sandy" <Evalenko.Sandy@epa.gov>, "Nasir, Iqra" <nasir.iqra@epa.gov>
> **Cc:** "Ruf, Christine" <Ruf.Christine@epa.gov>
> **Subject: FW: Perchlorate public comment period extension requests**
>
> FYI, we'll be seeing an FRN shortly to extend the comment period on perchlorate.
>
> ---
>
> **From:** Campbell, Ann
> **Sent:** Monday, October 02, 2017 10:49 AM
> **To:** Lousberg, Macara <Lousberg.Macara@epa.gov>
> **Subject:** Fw: Perchlorate public comment period extension requests
>
> ---
>
> **From:** Forsgren, Lee
> **Sent:** Sunday, October 1, 2017 5:47 PM
> **To:** Mclain, Jennifer
> **Cc:** Shapiro, Mike; Grevatt, Peter; Campbell, Ann; Best-Wong, Benita; Burneson, Eric
> **Subject:** Re: Perchlorate public comment period extension requests
>
> Both Sarah and I concur and if you cc me on the FR package I will reach out it OP on the notice.
>
> Sent from my iPhone
>
> On Oct 1, 2017, at 11:37 AM, Mclain, Jennifer <Mclain.Jennifer@epa.gov> wrote:
>
>> Thanks Mike. We plan to have the FRN and letter responses into review early this week.
>>
>> Jennifer

On Oct 1, 2017, at 11:32 AM, Shapiro, Mike <Shapiro.Mike@epa.gov> wrote:

> I think you should proceed, given the timing. We will probably need an affirming note from Lee, but since he has already concurred that shouldn't be an issue.
>
> Mike
>
> Michael Shapiro
> Deputy Assistant Administrator
> US EPA, Office of Water
>
> On Sep 29, 2017, at 11:36 AM, Grevatt, Peter <Grevatt.Peter@epa.gov> wrote:
>
>> First, we'll appreciate your input on whether we need to seek input from the AO on this approach as well. If we are good to move forward, we would communicate with the organizations that submitted the requests informally, then we'll need to draft formal response letters and quickly put together the FR notices that will be needed to modify the public comment periods. We'll certainly need your help to get these approved quickly.
>>
>> ---
>>
>> **From:** Shapiro, Mike
>> **Sent:** Friday, September 29, 2017

11:19 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Campbell, Ann <Campbell.Ann@epa.gov>; Best-Wong, Benita <Best-Wong.Benita@epa.gov>
Subject: FW: Perchlorate public comment period extension requests

Jennifer and Peter,

Both Lee and I are on board with your recommendations on the Perchlorate extension requests. What's the next step?

Mike

Michael Shapiro

Acting Assistant Administrator, Office of Water

US EPA, 4101M

1200 Pennsylvania Ave., NW

Washington, DC 20460

202-564-5700

From: Forsgren, Lee
Sent: Friday, September 29, 2017 7:09 AM
To: Shapiro, Mike <Shapiro.Mike@epa.gov>
Subject: Re: Perchlorate public comment period extension requests

Mike

Those are parameters that I talked about with them so I would agree as well.

Lee

Sent from my iPhone

On Sep 28, 2017, at 11:24 PM, Shapiro, Mike <Shapiro.Mike@epa.gov> wrote:

> Lee,
>
> I'm suppo rtive of the OGW

DW recommendation, which is no extension for the comment period on the charge and panel members and 21 day extension for the comment period on the report. This is the most we can do without further delaying our schedule, which is already extremely challenging.

Mike

Michael Shapiro

Acting Assistant Administrator, Office of Water

US EPA, 4101 M

1200 Pennsylvania Ave., NW

Washington, DC 20460

202-564-5700

From: Mclain, Jennifer
Sent: Thursday, September

28,
2017
1:07
PM
To:
Forsgr
en, Lee
<Forsg
ren.Le
e@epa
.gov>
Cc:
Shapir
o,
Mike
<Shapi
ro.Mik
e@epa
.gov>;
Best-
Wong,
Benita
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Benita
@epa.
gov>;
Grevat
t,
Peter
<Greva
tt.Pete
r@epa.
gov>;
Burnes
on,
Eric
<Burne
son.Eri
c@epa
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Campb
ell,
Ann
<Camp
bell.An
n@epa
.gov>;
Tiago,

Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>

Subject: Perchlorate public comment period extension requests

Lee,

As discussed, here is a paper providing potential option

s for EPA's response to extension requests on the perchlorate peer review materials.

Please let me know if you would like to discuss further or if you have any questions. We are also working on communications for an extension announcement as well as on missing the upcoming

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Jennife
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Jennife
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McLain
, Ph.D.

Acting
Deputy
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of
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Water

U.S.
EPA

202-
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Ms. Judith Nordgren
Managing Director
Chlorine Chemistry Division
American Chemistry Council

Dear Ms. Nordgren:

Thank you for your letter dated September 26, 2017, which requests a 45-day extension to the comment period for the draft report "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water". On September 15, 2017, EPA published a *Federal Register* notice providing a 45-day public comment period for this action.

After reviewing your request, EPA agrees to grant a 21-day extension on the comment period which will now end on November 20, 2017. The extension will allow additional time for stakeholders to provide comments on the scientific materials, while not delaying EPA's progress completing the peer review process. The EPA is committed to using the best available peer reviewed science to inform Safe Drinking Water Act decision-making on perchlorate.

Peter Grevatt, Director
Office of Ground Water and Drinking Water
Office of Water

Mr. G. Tracy Mehan, III
Executive Director – Government Affairs
American Water Works Association

Dear Mr. Mehan:

Acting Assistant Administrator Shapiro asked me to respond to your letter dated September 20, 2017, which requests a 45-day extension to the comment period for the draft report "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water". On September 15, 2017, EPA published a *Federal Register* notice providing a 45-day public comment period for this action.

After reviewing your request, EPA agrees to grant a 21-day extension on the comment period which will now end on November 20, 2017. The extension will allow additional time for stakeholders to provide comments on the scientific materials, while not delaying EPA's progress completing the peer review process. The EPA is committed to using the best available peer reviewed science to inform Safe Drinking Water Act decision-making on perchlorate.

Peter Grevatt, Director
Office of Ground Water and Drinking Water
Office of Water

Ms. Erica Bernstein
Director - Outreach
The Chlorine Institute

Dear Ms. Bernstein:

Thank you for your letter dated September 27, 2017, which requests an extension of 75-days for the comment period on the draft report "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (i.e., MCLG Approaches Report), and an extension of 45-days on the interim list of perchlorate in drinking water expert peer reviewers and draft peer review charge questions.

In your letter, you express concern that the public comment periods are inadequate due to the technical complexity and volume of the materials. After reviewing your request, EPA agrees to provide an additional 21 days for public review and comment on the draft MCLG Approaches Report, which will allow for submission of comments through November 20, 2017. However, the Agency does not believe an extension of the comment period for the draft list of expert peer reviewers and charge questions is warranted. The Agency does not believe that additional time is needed to comment on the list of expert peer reviewers and charge questions. There have been previous opportunities for public nominations for potential peer reviewers and EPA is confident that the interim list contains experts with the appropriate technical backgrounds for the perchlorate peer review effort.

The EPA is committed to using the best available science to inform Safe Drinking Water Act decision making for perchlorate and doing so in a timely manner. Completion of the expert peer review of these important scientific materials is a critical step in furthering public health protection.

Peter Grevatt, Director
Office of Ground Water and Drinking Water
Office of Water

Mr. Tom Roberts
Perchlorate Study Group Counsel
Van Ness Feldman, LLP

Dear Mr. Roberts:

Acting Assistant Administrator Shapiro asked me to respond to your letter dated September 26, 2017, which requests an extension of 75-days for the comment period on the draft report "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (i.e., MCLG Approaches Report), and an extension of 45-days on the interim list of perchlorate in drinking water expert peer reviewers and draft peer review charge questions.

In your letter you express concern that the public comment periods are inadequate due to the technical complexity and volume of the materials. After reviewing your request, EPA agrees to provide an additional 21 days for public review and comment on the draft MCLG Approaches Report, which will allow for submission of comments through November 20, 2017. However, the Agency does not believe an extension of the comment period for the draft list of expert peer reviewers and charge questions is warranted. The Agency does not believe that additional time is needed to comment on the list of expert peer reviewers and charge questions. There have been previous opportunities for public nominations for potential peer reviewers and EPA is confident that the interim list contains experts with the appropriate technical backgrounds for the perchlorate peer review effort.

The EPA is committed to using the best available science to inform Safe Drinking Water Act decision making for perchlorate and doing so in a timely manner. Completion of the expert peer review of these important scientific materials is a critical step in furthering public health protection.

Peter Grevatt, Director
Office of Ground Water and Drinking Water
Office of Water

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 2/24/2020 2:12:33 AM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Revised Document
Attachments: Perchlorate Recommendations for PWS 2-21-20.docx; Perchlorate Reductions 2-19-20 v1.docx

Thank you Eric & Lisa – The attached contain a very few edits/comments. And then, these are ready to go to OW for review. Regarding the outreach plan, continue to pursue the discussions with ASDWA and AWWA as we discussed and agreed to with Dave. However, I'm not sure that we can say these reports will be released soon, maybe it is better to say that there is the potential for them to be issued in the near term.

Thanks much,
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 21, 2020 10:15 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Thursday, February 20, 2020 4:19 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Jennifer;

Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Wednesday, February 12, 2020 11:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Grevatt, Peter [Grevatt.Peter@epa.gov]
Sent: 3/30/2017 12:46:02 PM
To: Best-Wong, Benita [Best-Wong.Benita@epa.gov]
CC: Shapiro, Mike [Shapiro.Mike@epa.gov]; Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Ruf, Christine [Ruf.Christine@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Materials needed
Attachments: One_pager_Perchlorate in drinking water_fv_32217.doc

Benita, here is the one pager we sent up last week on perchlorate. I think this is the most succinct and current status of the action. Please let us know if a more extensive background paper is needed.

From: Best-Wong, Benita
Sent: Thursday, March 30, 2017 7:46 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Cc: Ruf, Christine <Ruf.Christine@epa.gov>
Subject: Materials needed

Peter,
As a follow up from Mike's general with Sarah yesterday, she would like a background paper on perchlorate. I'm hoping that you have something already prepared that I can provide to her. I'm also copying Christine in case she has something already available.
Benita

Benita Best-Wong
Acting Deputy Assistant Administrator
Office of Water
US EPA
1200 Pennsylvania Avenue, NW
Washington, DC 20460
202-566-1159

Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN 2040-AF28, significant

Purpose: To improve the health protection from perchlorate in drinking water.

Background: On February 11, 2011, EPA announced its decision to regulate perchlorate based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant. SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013) and finalize the regulations 18 months after proposal (can extend up to 9 months).

Stakeholder Involvement: EPA consulted with the National Drinking Water Advisory Council in 2012 on potential requirements of the perchlorate regulation. EPA has also met or corresponded with industry groups including the Perchlorate Study Group, American Chemistry Council, the American Water Works Association and the U.S. Chamber of Commerce. EPA was sued by the Natural Resources Defense Council in 2016 for the Agency's failure to issue proposed and final regulations for perchlorate in accordance with SDWA timelines.

Key Issues/Internal Review: The key issue for perchlorate is establishing the Maximum Contaminant Level Goal (MCLG[1]) which is defined in SDWA as the "level at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety." In early 2012, the Agency sought recommendations from EPA's Science Advisory Board on how to derive a MCLG for perchlorate in accordance with SDWA. The SAB recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling." In response to SAB recommendations, FDA and EPA scientists worked to develop models to relate perchlorate exposure to biological effects to infants and other life stages. EPA completed an expert peer review of the models, and we are preparing for a second expert peer review of methodologies to apply the model to identify potential MCLGs for perchlorate. Once peer review of these analyses are completed, OW will brief the Administrator and seek input on the level at which the MCLG should be set and whether the Agency should proceed with a perchlorate rulemaking (EPA reads the SDWA to allow the Agency to withdraw the determination to regulate through a new round of notice and comment rulemaking).

Legal Deadlines: EPA is under a consent decree with enforceable dates of October 31, 2018 for signature of a proposed MCLG and NPDWR and a signature date of December 19, 2019 for the final MCLG and NPDWR for perchlorate.

Timing: In order to complete necessary analyses for development of a proposed rule, including the Heath Risk Reduction Cost Analysis required by SDWA, we will need to initiate expert peer review of the approaches to derive an MCLG in mid May and complete the review in October 2017. We would like to brief the A.O. about peer review in April.

---

[1] Maximum Contaminant Level Goal (MCLG) is a non-enforceable public health goal. The enforceable standard, the Maximum Contaminant Level (MCL) is set as close to the MCLG as feasible using best available treatment technology and taking cost into consideration.

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 3/6/2020 3:49:19 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: FW: Materials for Briefing: Perchlorate
Attachments: Option Selection for Perchlorate_final_01.09.2020.pdf; Decision for Perchlorate Final Regulatory Action_3-3-20_clean.docx

Joe
The attached briefing materials for the Administrator are gtg. Our intent is to also provide the 2 perchlorate documents currently under OW review. It would be helpful to know whether OW has further comments on those documents so we can address prior to the meeting with the Administrator.
Thanks!
Jennifer

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 10/4/2017 3:44:58 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension
Attachments: ACC request for comment period extension_perchlorate 9-26-17.pdf; psg - 2nd peer review - comment period extension request - 9.26.17.pdf; AWWA MCLG Approach Comment Extension Request.pdf; Chlorine Institute Request for Comment Period Extension.pdf

Eric – please see highlighted note below regarding calls to extension requesters. I assume you'll also call the folks that sent letters to Sam??
For reference, letters attached.

AWWA – Tracy Mehan 202-628-8303
ACC – Judith Nordgren 202-249-7000
Chlorine Institute – Erica Bernstein 703-894-4114
PSG/Van Ness Feldmann – Tom Roberts 202-298-1800

From: Tiago, Joseph
Sent: Wednesday, October 04, 2017 11:32 AM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

Hi Crystal,

I checked with Peter:

- Eric to make a phone contact to the organizations that submitted the request to Mike and tell them that a FRN will come out soon with an extension of the public comment period. – This can be done as soon as today since Mike signed the package.

- SRMD to draft a formal letter response to those entities for Peter to sign on behalf of Mike. – The letter should state that Mike asked Peter to respond. Let coordinate on this.

Thanks,

Joe.

From: Rodgers-Jenkins, Crystal
Sent: Wednesday, October 4, 2017 10:08 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

On Sept 29th, Peter wrote to Mike (see email chain below)

First, we'll appreciate your input on whether we need to seek input from the AO on this approach as well. If we are good to move forward, we would communicate with the organizations that submitted the requests informally, then we'll need to draft formal response letters and quickly put together the FR notices that will be needed to modify the public comment periods. We'll certainly need your help to get these approved quickly.

I am checking in so that we can all be clear on who will informally communicate to the organizations about our response to their request. I am guessing the calls would need to happen this week. My understanding is that the FR notice went upstairs this morning and we expect the FR to be published next week.

I've asked Lisa to draft a few talking points in case Peter is planning to make the calls. We are fine with making the calls if Peter wishes to delegate to SRMD management.

Please let us know.

Take care,
Crystal

From: Burneson, Eric
Sent: Tuesday, October 03, 2017 8:06 AM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Fwd: Perchlorate public comment period extension requests

Crystal
I have not yet reviewed this notice. Can you please review and move forward as soon as Lisa gets this to you?
Thanks

Sent from my iPhone

Begin forwarded message:

> **From:** "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Date:** October 2, 2017 at 1:43:46 PM EDT
> **To:** "Flaharty, Stephanie" <Flaharty.Stephanie@epa.gov>
> **Cc:** "Christ, Lisa" <Christ.Lisa@epa.gov>, "Huff, Lisa" <Huff.Lisa@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>, "Tiago, Joseph" <Tiago.Joseph@epa.gov>, "Tricas, Marisa" <tricas.marisa@epa.gov>
> **Subject: Re: Perchlorate public comment period extension requests**
>
> Great. I will Lee know we are aiming for his review on Thursday.
>
> Jennifer
>
> On Oct 2, 2017, at 11:50 AM, Flaharty, Stephanie <Flaharty.Stephanie@epa.gov> wrote:
>
> > Thanks Lisa !

From: Christ, Lisa
Sent: Monday, October 02, 2017 12:49 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Huff, Lisa <Huff.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
Subject: RE: Perchlorate public comment period extension requests

Hi Stephanie,
Sam already drafted a notice that I reviewed – he's getting OGC concurrence. He also drafted transmittal memos. WE should be circulating them for review soon.
Lisa

From: Flaharty, Stephanie
Sent: Monday, October 02, 2017 12:40 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
Subject: FW: Perchlorate public comment period extension requests

Jennifer,

I have an FR template that we used for the last extension so I can draft the new notice. **Please let me know how much time we're are granting for the extension.**

Peter can sign the notice but we need to clear FRNs through OP prior to signature. Mike is out all week and Lee is in the office this Thursday and Friday. He is on travel all next week so this Thursday is our opportunity to have him send an email to clear the FRN through OP and higher. I'll need to end OW the draft FRN and action information sheet by Thursday morning and Macara will request that Lee clear it before he goes on travel next week.

Please let me know if you all can work with the timing.

Thanks,
Steph

Begin forwarded message:

> **From:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
> **Date:** October 2, 2017 at 10:51:50 AM EDT
> **To:** "Evalenko, Sandy" <Evalenko.Sandy@epa.gov>, "Nasir, Iqra" <nasir.iqra@epa.gov>
> **Cc:** "Ruf, Christine" <Ruf.Christine@epa.gov>
> **Subject: FW: Perchlorate public comment period extension requests**
>
> FYI, we'll be seeing an FRN shortly to extend the comment period on perchlorate.

From: Campbell, Ann
Sent: Monday, October 02, 2017 10:49 AM
To: Lousberg, Macara <Lousberg.Macara@epa.gov>
Subject: Fw: Perchlorate public comment period extension requests

---

From: Forsgren, Lee
Sent: Sunday, October 1, 2017 5:47 PM
To: Mclain, Jennifer
Cc: Shapiro, Mike; Grevatt, Peter; Campbell, Ann; Best-Wong, Benita; Burneson, Eric
Subject: Re: Perchlorate public comment period extension requests

Both Sarah and I concur and if you cc me on the FR package I will reach out it OP on the notice.

Sent from my iPhone

On Oct 1, 2017, at 11:37 AM, Mclain, Jennifer <Mclain.Jennifer@epa.gov> wrote:

> Thanks Mike. We plan to have the FRN and letter responses into review early this week.
>
> Jennifer
>
> On Oct 1, 2017, at 11:32 AM, Shapiro, Mike <Shapiro.Mike@epa.gov> wrote:
>
>> I think you should proceed, given the timing. We will probably need an affirming note from Lee, but since he has already concurred that shouldn't be an issue.
>>
>> Mike
>>
>> Michael Shapiro
>> Deputy Assistant Administrator
>> US EPA, Office of Water
>>
>> On Sep 29, 2017, at 11:36 AM, Grevatt, Peter <Grevatt.Peter@epa.gov> wrote:
>>
>>> First, we'll appreciate your input on

whether we need to seek input from the AO on this approach as well. If we are good to move forward, we would communicate with the organizations that submitted the requests informally, then we'll need to draft formal response letters and quickly put together the FR notices that will be needed to modify the public comment periods. We'll certainly need your help to get these approved quickly.

From: Shapiro, Mike
Sent: Friday, September 29, 2017 11:19 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Campbell, Ann <Campbell.Ann@epa.gov>; Best-Wong, Benita <Best-Wong.Benita@epa.gov>
Subject: FW: Perchlorate public comment period extension requests

Jennifer and Peter,

Both Lee and I are on board with your recommendations on the Perchlorate extension requests. What's the next step?

Mike

Michael Shapiro

Acting Assistant Administrator, Office of Water

US EPA, 4101M

1200 Pennsylvania Ave., NW

Washington, DC 20460

202-564-5700

From: Forsgren, Lee
Sent: Friday, September 29, 2017 7:09 AM
To: Shapiro, Mike <Shapiro.Mike@epa.gov>
Subject: Re: Perchlorate public comment period extension requests

Mike

Those are parameters that I talked about with them so I would agree as well.

Lee

Sent from my iPhone

On Sep 28, 2017, at 11:24 PM, Shapiro, Mike <Shapiro.Mike@epa.gov> wrote:

> Lee,
>
> I'm supportive of the OGWDW recommendation, which is no extension for the comment period on the charge and panel members and 21 day extension for the

comment period on the report. This is the most we can do without further delaying our schedule, which is already extremely challenging.

Mike

Michael Shapiro

Acting Assistant Administrator, Office of Water

US EPA, 4101 M

1200 Pennsylvania Ave., NW

Washington, DC 20460

202-564-5700

From: Mclain, Jennifer
Sent: Thursday, September 28, 2017 1:07 PM
To: Forsgren, Lee <Forsgren.Lee@epa.gov>
Cc: Shapiro, Mike <Shapiro.Mike@epa.gov>; Best-Wong, Benita

<Best-Wong.Benita@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Campbell, Ann <Campbell.Ann@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>

Subject: Perchl

orate public comm ent period extensi on reques ts

Lee,

As discuss ed, here is a paper providi ng potenti al option s for EPA's respon se to extensi on reques ts on the perchl orate peer review materi als.

Please let me know if you would like to

discuss further or if you have any questi ons. We are also workin g on comm unicati ons for an extensi on annou nceme nt as well as on missin g the upcom ing consen t decree date for compl eting the peer review.

Jennife r

Jennifer L McLain, Ph.D.

Acting Deputy Director

Office of Ground Water and Drinking Water

U.S. EPA

202-564-4029

<Perchlorate peer reveiw extension options.docx>

American Water Works Association

Dedicated to the World's Most Important Resource®

Government Affairs Office
1300 Eye Street NW, Suite 701W
Washington, DC 20005-3314
T 202.628.8303
F 202.628.2846

September 20, 2017

SUBMITTED VIA E-MAIL

Mr. Michael H. Shapiro,
U.S. Environmental Protection Agency
Office of Water
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

RE: Request for Comment Period Extension on the draft report entitled, "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (82 FR 43354; EPA–HQ–OW–2016–0438)

Dear Mr. Shapiro:

The American Water Works Association (AWWA) respectfully requests that EPA extend the comment period on the draft report, "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", by 45-days to December 14, 2017. Given the complexity of the revisions in the Biologically Based Dose-Response (BBDR) model, we believe that a 90-day comment period in necessary to provide a reasonable opportunity for public review and comment.

We support EPA's responsiveness to elvaluating the recommendations made by the peer review panel in January 2017. Both the public and the next peer review panel will benefit from additional time to examine the modifications and technical assumptions embedded in the new BBDR model. We respectfully request a 45-day extension to support the public's consideration of the BBDR models scientific rigor and efficacy.

We would appreciate a response to this request as soon as possible. Should you have questions or would like to discuss this matter, please contact me (tmehan@awwa.org) or Kevin Morley (kmorley@awwa.org).

Yours Sincerely,

G. Tracy Mehan, III
Executive Director – Government Affairs

cc: Lee Forsgren – EPA, OW
Peter Grevatt – EPA, OGWDW
Eric Burneson – EPA, OGWDW
Samuel Hernandez – EPA, OGWDW

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 1/15/2020 5:35:07 PM
To: Bradford, Charlotte [Bradford.Charlotte@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Behl, Betsy [Behl.Betsy@epa.gov]; Flaherty, Colleen [Flaherty.Colleen@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Wang, Lili [Wang.Lili@epa.gov]; Hautman, Dan [Hautman.Dan@epa.gov]; Carroll, Gregory [Carroll.Gregory@epa.gov]; Albert, Ryan [Albert.Ryan@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]
CC: Reiley, Mary [Reiley.Mary@epa.gov]; Greene, Sophie [greene.sophie@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Forrest, Kesha [Forrest.Kesha@epa.gov]
Subject: RE: SRMD/HECD Coordination
Attachments: Draft Perchlorate Compendium.docx; PERCHLORATE - SRMD&HECD.v2.docx

DRAFT -- INTERNAL DELIBERATIVE

All,
Attached is the current schedule for the tentative decision by Administrator Wheeler to withdraw the reg det. I've also attached the compendium of public comments. For the withdraw option, we can limit the scope of public comment topics we need to address. We are confirming this with OGC since our attorney has changed. We believe the topics we'll need to respond to include: withdrawing the reg det; the interim health advisory; health effects; and SDWA authority. I've highlighted the topics where we'll need OST support.
Lisa

-----Original Appointment-----
From: Bradford, Charlotte <Bradford.Charlotte@epa.gov>
Sent: Thursday, October 03, 2019 11:16 AM
To: Bradford, Charlotte; Burneson, Eric; Behl, Betsy; Flaherty, Colleen; Rodgers-Jenkins, Crystal; Huff, Lisa; Wang, Lili; Hautman, Dan; Carroll, Gregory; Albert, Ryan; Christ, Lisa; Strong, Jamie
Cc: Reiley, Mary; Greene, Sophie; Miller, Gregory; Forrest, Kesha
Subject: SRMD/HECD Coordination
When: Wednesday, January 15, 2020 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomEast2339/DC-ICC-OW-OGWDW

CONFERENCE CALL-IN #866-299-3188 **CODE:** Ex. 6 Personal Privacy (PP)

AGENDA

- CCL5 Update
- Perchlorate NPDWR—FY 20 Plan
  - Schedule
  - Inputs and Deliverables needed from HECD

Please identify any other topics to be covered.

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/19/2020 10:28:22 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: 2 perchlorate documents -- for your records
Attachments: Perchlorate Reductions 2-19-20 v1.docx; Perchlorate Recommendations for PWS_formatcw.v2.docx

Hi Eric,

Here are the revised versions of the Perchlorate Documents.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 19, 2020 4:49 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thanks Sam. This is good to go. Can you send me the clean version. Also would you mind sending a clean version of the other document in the same email?
Thanks
Eric

From: Hernandez-Quinones, Samuel
Sent: Tuesday, February 18, 2020 1:54 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Hi Eric,

Here is the revised redline version of the document. Let me know if you have additional comments or suggested edits.

If there are no additional edits required, please let me know and I will send you a clean version.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 18, 2020 11:19 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thank you Sam and Rajiv for your work to address my comments. I have a few more follow up request in the attached. Can you see if we can get OLEM to expedite their feedback on the table? Putting forward this document is critical to getting decisions needed to make the court filing.
Eric

From: Hernandez-Quinones, Samuel
Sent: Tuesday, February 18, 2020 10:23 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Hi Eric, please see attached document. It incorporates your suggested edits and addresses your questions.

I am also waiting for some additional feedback form OSWER on the table they provided, as they way it reads now it appears to show several entries for the same mitigation site. Depending on their feedback we might have to update that table.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Tuesday, February 18, 2020 10:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Yes I'll check with Sam and get back to you.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 18, 2020 10:07 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: 2 perchlorate documents -- for your records

Lisa:
I sent the attached comments to Lisa Christ on Thursday but I don't think I received a revised document. Since Lisa is out today, can you check with the Team to get me a revised today?
Thanks
Eric

From: Burneson, Eric
Sent: Thursday, February 13, 2020 2:05 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thank You Lisa
I have a few comments/edits on the perchlorate reduction document in the attached.
Eric

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: 2 perchlorate documents -- for your records

Eric – just wanted to put both documents in one place for you. Both have been reviewed by Jennifer and Christina. Lisa

---

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 10/4/2017 2:48:40 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

Hi All,

There is a typo highlighted in the email below. The extended comment period now ends on November 20. It indicates November 30 in the note below.

Thanks
Sam

From: Christ, Lisa
Sent: Wednesday, October 04, 2017 10:42 AM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

Letters are attached

Requesters for extension of just the report comment period by 45 days:
AWWA – request to Mike Shapiro
American Chemistry Council – request to Sam Hernandez

- Thanks for your continued interest in perchlorate in drinking water
- You sent a letter requesting an extension of 45 days of the comment period for the draft report "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water"
- I understand that the BBDR model revisions and analysis in the MCLG Aproaches Report represent complex analysis that require carfeul review.
- I believe that peer review is an important component of the scientific process to assure the use of the best available science, strengthen the interpretation of the reviewed material, and add credibility to the analysis.
- Although I'm not able to extend the public comment period by the full 45 days, EPA can extend it by 21 days – giving reviewers until November 30 to submit comments.
- I believe this will provide adequate time for review and comment while allowing EPA to work to meet deadlines established under the consent decree.

Requesters for extension of both comment periods; 45 days for peer reviewers and charge & 75 days for the report
PSG – request to Mike Shapiro
The Chlorine Institute – request to Sam Hernandez

- Thanks for your continued interest in perchlorate in drinking water
- You sent a letter requesting an extension of 75 days for the comment period for the draft report "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water"
- Your letter also requested a 45 day extension of the public comment period for the draft list of peer reviewers and draft charge

- I understand that the BBDR model revisions and analysis in the MCLG Aproaches Report represent complex analysis that require carfeul review.
- I believe that peer review is an important component of the scientific process to assure the use of the best available science, strengthen the interpretation of the reviewed material, and add credibility to the analysis.
- Unfortunately EPA is not able to extend the comment period for the list of reviewers and the charge, stakeholders have had opportunity for input through the nominations process.
- I can extend the public comment period for the draft MCLG Approaches Report by 21 days.
- I believe this will provide adequate time for review and comment while allowing EPA to work to meet deadlines established under the consent decree.

From: Rodgers-Jenkins, Crystal
Sent: Wednesday, October 04, 2017 10:08 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Perchlorate public comment period extension requests - communicating informally to the organizations that requested an extension

On Sept 29th, Peter wrote to Mike (see email chain below)

First, we'll appreciate your input on whether we need to seek input from the AO on this approach as well. If we are good to move forward, we would communicate with the organizations that submitted the requests informally, then we'll need to draft formal response letters and quickly put together the FR notices that will be needed to modify the public comment periods. We'll certainly need your help to get these approved quickly.

I am checking in so that we can all be clear on who will informally communicate to the organizations about our response to their request. I am guessing the calls would need to happen this week. My understanding is that the FR notice went upstairs this morning and we expect the FR to be published next week.

I've asked Lisa to draft a few talking points in case Peter is planning to make the calls. We are fine with making the calls if Peter wishes to delegate to SRMD management.

Please let us know.

Take care,
Crystal

From: Burneson, Eric
Sent: Tuesday, October 03, 2017 8:06 AM
To: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Fwd: Perchlorate public comment period extension requests

Crystal
I have not yet reviewed this notice. Can you please review and move forward as soon as Lisa gets this to you?
Thanks

Sent from my iPhone

Begin forwarded message:

From: "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
Date: October 2, 2017 at 1:43:46 PM EDT
To: "Flaharty, Stephanie" <Flaharty.Stephanie@epa.gov>
Cc: "Christ, Lisa" <Christ.Lisa@epa.gov>, "Huff, Lisa" <Huff.Lisa@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>, "Tiago, Joseph" <Tiago.Joseph@epa.gov>, "Tricas, Marisa" <tricas.marisa@epa.gov>
Subject: Re: Perchlorate public comment period extension requests

Great. I will Lee know we are aiming for his review on Thursday.

Jennifer

On Oct 2, 2017, at 11:50 AM, Flaharty, Stephanie <Flaharty.Stephanie@epa.gov> wrote:

Thanks Lisa !

From: Christ, Lisa
Sent: Monday, October 02, 2017 12:49 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Huff, Lisa <Huff.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
Subject: RE: Perchlorate public comment period extension requests

Hi Stephanie,
Sam already drafted a notice that I reviewed – he's getting OGC concurrence. He also drafted transmittal memos. WE should be circulating them for review soon.
Lisa

From: Flaharty, Stephanie
Sent: Monday, October 02, 2017 12:40 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
Subject: FW: Perchlorate public comment period extension requests

Jennifer,

I have an FR template that we used for the last extension so I can draft the new notice. **Please let me know how much time we're are granting for the extension.**

Peter can sign the notice but we need to clear FRNs through OP prior to signature. Mike is out all week and Lee is in the office this Thursday and Friday. He is on travel all next week so this Thursday is our opportunity to have him send an email to clear the FRN through OP and higher. I'll need to end OW the draft FRN and action information sheet by Thursday morning and Macara will request that Lee clear it before he goes on travel next week.

Please let me know if you all can work with the timing.

Thanks,
Steph

Begin forwarded message:

From: "Lousberg, Macara" <Lousberg.Macara@epa.gov>
Date: October 2, 2017 at 10:51:50 AM EDT
To: "Evalenko, Sandy" <Evalenko.Sandy@epa.gov>, "Nasir, Iqra" <nasir.iqra@epa.gov>
Cc: "Ruf, Christine" <Ruf.Christine@epa.gov>
Subject: FW: Perchlorate public comment period extension requests

FYI, we'll be seeing an FRN shortly to extend the comment period on perchlorate.

From: Campbell, Ann
Sent: Monday, October 02, 2017 10:49 AM
To: Lousberg, Macara <Lousberg.Macara@epa.gov>
Subject: Fw: Perchlorate public comment period extension requests

---

From: Forsgren, Lee
Sent: Sunday, October 1, 2017 5:47 PM
To: Mclain, Jennifer
Cc: Shapiro, Mike; Grevatt, Peter; Campbell, Ann; Best-Wong, Benita; Burneson, Eric
Subject: Re: Perchlorate public comment period extension requests

Both Sarah and I concur and if you cc me on the FR package I will reach out it OP on the notice.

Sent from my iPhone

On Oct 1, 2017, at 11:37 AM, Mclain, Jennifer <Mclain.Jennifer@epa.gov> wrote:

> Thanks Mike. We plan to have the FRN and letter responses into review early this week.
>
> Jennifer
>
> On Oct 1, 2017, at 11:32 AM, Shapiro, Mike <Shapiro.Mike@epa.gov> wrote:

I think you should proceed, given the timing. We will probably need an affirming note from Lee, but since he has already concurred that shouldn't be an issue.

Mike

Michael Shapiro
Deputy Assistant Administrator
US EPA, Office of Water

On Sep 29, 2017, at 11:36 AM, Grevatt, Peter <Grevatt.Peter@epa.gov> wrote:

> First, we'll appreciate your input on whether we need to seek input from the AO on this approach as well. If we are good to move forward, we would communicate with the organizations that submitted the requests informally, then we'll need to draft formal response letters and quickly put together the FR notices that will be needed to modify the public comment periods. We'll certainly need your help to get these approved quickly.
>
> ---
>
> **From:** Shapiro, Mike
> **Sent:** Friday, September 29, 2017 11:19 AM
> **To:** Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer

<Mclain.Jennifer@epa.gov>
Cc: Campbell, Ann <Campbell.Ann@epa.gov>; Best-Wong, Benita <Best-Wong.Benita@epa.gov>
Subject: FW: Perchlorate public comment period extension requests

Jennifer and Peter,

Both Lee and I are on board with your recommendations on the Perchlorate extension requests. What's the next step?

Mike

Michael Shapiro

Acting Assistant Administrator, Office of Water

US EPA, 4101M

1200 Pennsylvania Ave., NW

Washington, DC 20460

202-564-5700

From: Forsgren, Lee
Sent: Friday, September 29, 2017 7:09 AM
To: Shapiro, Mike <Shapiro.Mike@epa.gov>
Subject: Re: Perchlorate public comment period extension requests

Mike

Those are parameters that I talked about with them so I would agree as well.

Lee

Sent from my iPhone

On Sep 28, 2017, at 11:24 PM, Shapiro, Mike <Shapiro.Mike@epa.gov> wrote:

> Lee,
>
> I'm supportive of the OGWDW recommendation, which

is no extension for the comment period on the charge and panel members and 21 day extension for the comment period on the report. This is the most we can do without further delaying our schedule, which is already extremely challenging.

Mike

Michael Shapiro

Acting Assistant Administrator, Office of Water

US EPA, 4101 M

1200 Pennsylvania Ave., NW

Washington, DC 20460

202-564-5700

From: Mclain, Jennifer
Sent: Thursday, September 28, 2017 1:07

PM
To:
Forsgr
en, Lee
<Forsg
ren.Le
e@epa
.gov>
Cc:
Shapir
o,
Mike
<Shapi
ro.Mik
e@epa
.gov>;
Best-
Wong,
Benita
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gov>;
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Peter
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Burnes
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Eric
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c@epa
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ell,
Ann
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bell.An
n@epa
.gov>;
Tiago,
Joseph
<Tiago.
Joseph

@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>

Subject: Perchlorate public comment period extension requests

Lee,

As discussed, here is a paper providing potential options for EPA's respon

se to extensi on reques ts on the perchl orate peer review materi als.

Please let me know if you would like to discuss further or if you have any questi ons. We are also workin g on comm unicati ons for an extensi on annou nceme nt as well as on missin g the upcom ing consen t decree

date for completing the peer review.

Jennifer

Jennifer L McLain, Ph.D.

Acting Deputy Director

Office of Ground Water and Drinking Water

U.S. EPA

202-564-4029

<Perch
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options
.docx>

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 2/28/2020 3:34:10 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Materials for tomorrow's Briefing: Perchlorate
Attachments: Option Selection for Perchlorate_final_01.09.2020.pdf; Perchlorate Reductions 2-25-20 v2.docx; Perchlorate Recommendations for PWS 2-25-20 v2.docx; Decision for Perchlorate Final Regulatory Action_2_26_20.docx

With next steps on attachment 4

From: Christ, Lisa
Sent: Wednesday, February 26, 2020 4:32 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Materials for tomorrow's Briefing: Perchlorate

Eric,
Attached is the 1 pager cover sheet to go with the January briefing paper and the two requested documents. The schedules in the January brief are out of date. I can provide an updated withdrawal schedule, but we haven't updated the non-withdrawal schedule.

Perchlorate Schedule - Draft 2/24/2020			
Activity	**start**	**end**	**No. Days**

Ex. 5 AC/AWP/DP

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 26, 2020 1:31 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Materials for tomorrow's Briefing: Perchlorate

Attached is the briefing that was used for the Administrator discussion.

From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Wednesday, January 08, 2020 3:05 PM
To: Bolen, Brittany <bolen.brittany@epa.gov>; Jones, Lindsey <jones.lindsey@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Nagle, Deborah <Nagle.Deborah@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Ross, David P <ross.davidp@epa.gov>
Cc: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>; Penman, Crystal <Penman.Crystal@epa.gov>; Lovell, Will (William) <lovell.william@epa.gov>; Hilosky, Nick <Hilosky.Nick@epa.gov>; Brooks, Becky <Brooks.Becky@epa.gov>; Mutz, John (Fletcher) <mutz.john@epa.gov>; Christian, Megan <Christian.Megan@epa.gov>; Fitzmorris, Amanda <fitzmorris.amanda@epa.gov>
Subject: Materials for tomorrow's Briefing: Perchlorate

All,

The final document for tomorrow's Briefing: Perchlorate with the Administrator is attached.

Thank you,
Janita

Janita Aguirre – Special Assistant
U.S. Environmental Protection Agency | Office of Water
Phone: **(202) 566-1149** | Email: **aguirre.janita@epa.gov**

Subject: Briefing: Perchlorate
Location: Administrator's Office

Start: Thu 1/9/2020 2:15 PM
End: Thu 1/9/2020 3:00 PM

Organizer: Adm15Wheeler.Calendar
Required Attendees: David Ross (ross.davidp@epa.gov); Mclain, Jennifer; Dunlap, David; Orme-Zavaleta, Jennifer; Wright, Peter; Breen, Barry; Leopold, Matt (OGC); Fotouhi, David; Wehling, Carrie; Nagle, Deborah; Bolen, Brittany; Jones, Lindsey

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 3/5/2020 8:28:30 PM
To: McLain, Jennifer L. [McLain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: Materials for Briefing: Perchlorate
Attachments: Option Selection for Perchlorate_final_01.09.2020.pdf; Decision for Perchlorate Final Regulatory Action_3-3-20_clean.docx

Jennifer & Eric,
Attached is the revised cover page for the perchlorate briefing with the Administrator. Also, the January 9 option selection briefing is attached.

Lisa

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Tuesday, March 03, 2020 5:10 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Materials for tomorrow's Briefing: Perchlorate

A few comments in the attached. Do we have a briefing tomorrow?

Joe – any news on scheduling the Administrator briefing?

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, March 3, 2020 4:37 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Materials for tomorrow's Briefing: Perchlorate

Jennifer: Attached are the materials that we would add to the recommendations and reductions documents (that were transmitted to OW) for a discussion with the Administrator. We note that the schedules in the briefing we gave the Administrator on 1/9/20 are now out of date. Below is an update for the withdrawal schedule that assumes a meeting occurs on March 16.

Perchlorate Schedule - Draft 2/24/2020			
Activity	**start**	**end**	**No. Days**

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 2/26/2020 4:49:24 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
Subject: RE: Revised Document
Attachments: Perchlorate Reductions 2-25-20 v2.docx; Perchlorate Recommendations for PWS 2-25-20 v2.docx

Thank you all! These look great.

Joe – please send the attached versions forward to OW.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 26, 2020 8:21 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: Attached please find clean copies of the recommendations and reductions documents for perchlorate. We have incorporated your edits. Please note with respect to your question about CCR reporting of perchlorate monitoring

CCR regulations under 141.153.(d)(1) requires the CCR include data on detected contaminants subject to mandatory monitoring including

i. Contaminants subject to an MCL, action level, MRDL or TT
ii. Contaminants for which monitoring is required under the UCMR
iii. Disinfection byproducts or micriobial contaminants for which monitoring is required.

Therefore if a system monitors for perchlorate outside of UCMR there is no requirement to report it on the CCR. If a system monitored for perchlorate in the UCMR 1 and detected it, then they were required to report it on the CCR for the next 5 years because 141.153(d)(3)(ii) UCMR results "need only be included in CCR for 5 years from the date of last sample or until any of the contaminants becomes regulated and subject to routine monitoring requirements, whichever comes first."
ASDWA is making arrangements for us to speak with the impacted States on Friday and or Monday morning.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Sunday, February 23, 2020 9:13 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa

<Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Thank you Eric & Lisa – The attached contain a very few edits/comments. And then, these are ready to go to OW for review. Regarding the outreach plan, continue to pursue the discussions with ASDWA and AWWA as we discussed and agreed to with Dave. However, I'm not sure that we can say these reports will be released soon, maybe it is better to say that there is the potential for them to be issued in the near term.

Thanks much,
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 21, 2020 10:15 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Thursday, February 20, 2020 4:19 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Wednesday, February 12, 2020 11:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that

monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 2/28/2020 3:20:16 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Revised Document
Attachments: Perchlorate in DW.CB.pdf; Perchlorate Reductions 2-25-20 v2-lc.docx

Eric,
In response to Charlotte's questions:
Purpose of documents: At the option selection briefing, two documents were requested to inform decision making (see attachments 2 and 3).

1. A summary of factors that have resulted in a reduction of perchlorate occurrence in drinking water and an update on the mitigation actions and levels of perchlorate for the 15 water systems that OW estimates would exceed the lowest proposed MCL of 18 ppb based on UCMR1 monitoring data.

2. Actions water systems can take to address perchlorate in drinking water, such as monitor for perchlorate, add treatment or consider non-treatment alternatives to reduce perchlorate levels and best practices for communicating with customers.

   The Las Vegas Wash is the correct terminology

   "researchers" in the table of water systems are the authors of the papers cited.

   We considered the 2008 AWWA occurrence follow up report in the 2011 reg det. At that time we were evaluating a range of potential MCLs, including as low as 4 ppb.

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Thursday, February 27, 2020 12:38 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Revised Document

Please find attached Charlotte's comments on the perchlorate documents. Thanks!

From: Tiago, Joseph
Sent: Wednesday, February 26, 2020 1:03 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Revised Document

Sent. Thanks!

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Wednesday, February 26, 2020 11:49 AM

To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Revised Document

Thank you all! These look great.

Joe – please send the attached versions forward to OW.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 26, 2020 8:21 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: Attached please find clean copies of the recommendations and reductions documents for perchlorate. We have incorporated your edits. Please note with respect to your question about CCR reporting of perchlorate monitoring

CCR regulations under 141.153.(d)(1) requires the CCR include data on detected contaminants subject to mandatory monitoring including

i. Contaminants subject to an MCL, action level, MRDL or TT
ii. Contaminants for which monitoring is required under the UCMR
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Therefore if a system monitors for perchlorate outside of UCMR there is no requirement to report it on the CCR. If a system monitored for perchlorate in the UCMR 1 and detected it, then they were required to report it on the CCR for the next 5 years because 141.153(d)(3)(ii) UCMR results "need only be included in CCR for 5 years from the date of last sample or until any of the contaminants becomes regulated and subject to routine monitoring requirements, whichever comes first."
ASDWA is making arrangements for us to speak with the impacted States on Friday and or Monday morning.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Sunday, February 23, 2020 9:13 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Thank you Eric & Lisa – The attached contain a very few edits/comments. And then, these are ready to go to OW for review. Regarding the outreach plan, continue to pursue the discussions with ASDWA and AWWA as we discussed and

agreed to with Dave. However, I'm not sure that we can say these reports will be released soon, maybe it is better to say that there is the potential for them to be issued in the near term.

Thanks much,
Jennifer

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Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
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To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
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Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

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Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

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Subject: FW: Revised Document

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Thanks

Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

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Sent: Monday, February 10, 2020 10:31 AM
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Thanks,
Lisa

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Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

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Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Wehling, Carrie [Wehling.Carrie@epa.gov]
Sent: 1/7/2020 10:02:37 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
CC: Wendelowski, Karyn [wendelowski.karyn@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: Revised Perchlorate Briefing
Attachments: Option Selection for Perchlorate 1-9-20v2.docx

Ex. 5 AC/AWP/DP

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, January 07, 2020 4:54 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Cc: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Revised Perchlorate Briefing

Thanks Jennifer. Good catch.

Carrie are you okay with this?

From: Mclain, Jennifer
Sent: Tuesday, January 07, 2020 4:51 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Cc: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Revised Perchlorate Briefing

Eric – I added one more point regarding 2020 actions that could mitigate concern (I understood Dave wanted this point). I also made a few other minor changes including spacing, etc.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, January 7, 2020 3:23 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>

Cc: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: Revised Perchlorate Briefing

Ex. 5 AC/AWP/DP

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 1/7/2020 9:51:04 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
CC: Wendelowski, Karyn [wendelowski.karyn@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: Revised Perchlorate Briefing
Attachments: Option Selection for Perchlorate 1-9-20v2.docx

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Subject: Revised Perchlorate Briefing

Jennifer and Carrie:
Attached for your review and comment is a revised Perchlorate Option Selection briefing that reflects the direction I heard in the discussion today including;

Ex. 5 AC/AWP/DP

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/26/2020 12:25:34 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Revised Document
Attachments: Perchlorate Reductions 2-25-20 v1.docx; Perchlorate Recommendations for PWS 2-25-20 v1.docx

Hi Eric,

Here are the clean versions of the revised documents.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 25, 2020 5:30 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Sam
Your changes to the recommendations and reductions document are good. Can you please send clean versions for me to forward to Jennifer.
Please note that I plan to respond to her questions about UCMR and CCR with the following. Please double check the accuracy.

Jennifer: Attached please find clean copies of the recommendations and reductions documents for perchlorate. We have incorporated your edits. Please note with respect to your question about CCR reporting of perchlorate monitoring

CCR regulations under 141.153.(d)(1) requires the CCR include data on detected contaminants subject to mandatory monitoring including

i. Contaminants subject to an MCL, action level, MRDL or TT
ii. Contaminants for which monitoring is required under the UCMR
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Therefore if a system monitors for perchlorate outside of UCMR there is no requirement to report it on the CCR. If a system monitored for perchlorate in the UCMR 1 and detected it, then they were required to report it on the CCR for the next 5 years because
141.153(d)(3)(ii) UCMR results "need only be included in CCR for 5 years from the date of last sample or until any of the contaminants becomes regulated and subject to routine monitoring requirements, whichever comes first.".

From: Hernandez-Quinones, Samuel
Sent: Monday, February 24, 2020 3:38 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Hi Eric and Lisa,

Here are the revised perchlorate documents.

I have also attached a redacted table (about the systems updates) that we can share with outside stakeholders if needed. Let me know if you have any questions or additional comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
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Director of Standards and Risk Management
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U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Thursday, February 20, 2020 4:19 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
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From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/24/2020 8:38:02 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Revised Document
Attachments: Perchlorate Updates - Systems Table.docx; Perchlorate Reductions 2-24-20 v1.docx; Perchlorate Recommendations for PWS 2-24-20 v1.docx

Hi Eric and Lisa,

Here are the revised perchlorate documents.

I have also attached a redacted table (about the systems updates) that we can share with outside stakeholders if needed. Let me know if you have any questions or additional comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, February 24, 2020 11:38 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

From: McLain, Jennifer L.
Sent: Sunday, February 23, 2020 9:13 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Thank you Eric & Lisa – The attached contain a very few edits/comments. And then, these are ready to go to OW for review. Regarding the outreach plan, continue to pursue the discussions with ASDWA and AWWA as we discussed and agreed to with Dave. However, I'm not sure that we can say these reports will be released soon, maybe it is better to say that there is the potential for them to be issued in the near term.

Thanks much,
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 21, 2020 10:15 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Thursday, February 20, 2020 4:19 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Wednesday, February 12, 2020 11:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW

Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Update on Systems with Perchlorate detections between 18 and 90 ppb in UCMR 1 (2001-2005)

State	System Name	Range of UCMR 1 Results (ppb)[1]	Updated Perchlorate Information
Florida	Sebring Water (FL6280250)	ND-70	EPA contacted the Sebring system in January 2020. Operations personnel indicated that no follow-up/updated monitoring data for perchlorate is available.
Florida	Manatee County Utilities Dept (FL6411132)	ND-30	Researchers contacted the system to identify the source of perchlorate. System personnel attributed the sole perchlorate detection under UCMR1 to analytical error. System personnel indicated that three other quarterly samples collected under UCMR1 as well as other subsequent perchlorate sampling efforts were non-detect. Source: AWWA (2008)
Georgia	Oconee Co.-Watkinsville (GA2190000)	38 (single sample)	Researchers contacted the system and found that a perchlorate contaminated well was removed from service in 2003. The system indicates that perchlorate is no longer detected. Source: Luis et al. (2019)
Louisiana	St. Charles Water District 1 East Bank (LA1089001)	ND-24	EPA was not able to identify updated data on perchlorate levels for this system.
Maryland	City of Aberdeen (MD0120001)	ND-19	The system's 2018 Consumer Confidence Report (CCR) indicates that perchlorate was not detected. In addition, researchers contacted the system and found that there has been no detection of perchlorate since treatment was installed in 2009. Source: Luis et al. (2019)
Maryland	Chapel Hill - Aberdeen Proving Grounds (MD0120002)	ND-20	EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System

[1] Values have been rounded. ND describes a sampling event where perchlorate was not detected at or above the UCMR 1 minimum reporting level of 4 ppb.

State	System Name	Range of UCMR 1 Results (ppb)[1]	Updated Perchlorate Information
			personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water.
Mississippi	Hilldale Water District (MS0750005)	ND-20	EPA contacted the Hilldale System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.
New Mexico	Deming Municipal Water System (NM3528616)	15-20	Data from EPA's SDWIS/FED indicates that the entry point that reported detections in UCMR1 (Well #3) is now inactive (i.e., the contaminated source is no longer in use). Source: SDWIS/FED (2016).
Nevada	City of Henderson (NV0000076)	6-23	Researchers report that the perchlorate levels described in the system's CCR ranged from non-detect to 9.7 ppb. Source AWWA (2008).
Ohio	Fairfield City PWS (OH0900715)	6-27	EPA contacted the Fairfield City System in January 2020. Water system personnel indicated that follow-up monitoring conducted after UCMR1 between 2002 and 2003 at the entry point (18 samples) were non-detects (< 4 ppb). Almost all of the 50 raw water samples taken from source wells were non-detect results.
Ohio	Hecla Water Association-Plant PWS (OH4401612)	ND-32	EPA contacted the Hecla Water Association System in January 2020. Water system personnel indicated that that no follow-up/updated monitoring data for perchlorate is available.
Oklahoma	Enid (OK2002412)	ND-30	EPA reviewed Oklahoma's monitoring data and did not find any monitoring results reported for perchlorate.
Pennsylvania	Meadville Area Water Authority (PA6200036)	ND-33	EPA contacted the Meadville System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.
Puerto Rico	Utuado Urbano (PR0002702)	ND-420	EPA contacted the Puerto Rico Aqueduct and Sewer Authority (PRASA) in January

State	System Name	Range of UCMR 1 Results (ppb)[1]	Updated Perchlorate Information
			2019. PRASA personnel indicated that no updated monitoring data for perchlorate is available. *NOTE: The PRASA personnel stated that the Utuado water system was significantly impacted by hurricane Maria and monitoring records from years prior to 2017 were lost.*
Texas	City of Levelland (TX1100002)	ND-32	Researchers found that a water storage tank was the source of perchlorate contamination, the wells feeding the tank were tested by the state and perchlorate was not detected. The water tank was shut off from service. Source: Luis et al. (2019).

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 2/12/2020 2:58:50 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: 2 perchlorate documents -- for your records
Attachments: Perchlorate Reductions 2-10-20 v2.docx; Perchlorate Recommendations for PWS_formatcw.v2.docx

Eric – just wanted to put both documents in one place for you. Both have been reviewed by Jennifer and Christina. Lisa

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From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

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Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 11/19/2019 2:43:22 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: RE: Perchlorate briefing
Attachments: Option Selection for Perchlorate 11-19-19 v1.docx

Hi Eric,

I have incorporated your edits as well as the additional occurrence data provided by the Reg Det Team, and the new input from OGC.

Please take particular attention to the edits I made to the language you inserted in the "Rationale" section of Option 1. I made the edits considering the data provided by the Reg Det Team.

Let me know if you have any comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, November 15, 2019 2:16 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Sam I just sent you my comments on the previous version. Let me know if there are edits you made in your version that need to be incorporated into mine.

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Friday, November 15, 2019 2:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric,

I have updated the briefing document after talking with Lisa Huff about the additional edits you wanted to see in the document.

I have also incorporated OGCs input into this version of the briefing document, which contains language about their legal strategy and the implications on the schedule. Let me know if you have any comments or if you would like us to include any additional information.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----

From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Thursday, November 14, 2019 4:32 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Re: Perchlorate briefing

Thanks Sam. Looks like you have the relevant points other than Eric said we should put as an option the MCLG if 18 not the other values. I'll talk to you in the morning and we can see what Eric wants to see.

Lisa

> On Nov 14, 2019, at 3:51 PM, Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov> wrote:
>
> Hi Lisa,
>
> I sent a revised draft version of the briefing document to Eric earlier this week. We are waiting for additional input that OGC will provide to us. Here is the revised document, as reviewed by Lisa, that I shared with Eric. If you have additional information, I will be glad to incorporate into the document.
>
> I will be in the office tomorrow morning if you want to hand those notes to me, or you can also email them.
>
> Thanks
> Sam
> ==========
> Samuel Hernández Quiñones, P.E.
> Environmental Engineer
> Office of Water
> Environmental Protection Agency
> 1200 Pennsylvania Ave. NW
> Washington, DC 20460
> 202-564-1735
>
> "USEPA Protecting Human Health and the Environment"
>
> -----Original Message-----
> From: Huff, Lisa <Huff.Lisa@epa.gov>
> Sent: Thursday, November 14, 2019 3:37 PM
> To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
> Cc: Christ, Lisa <Christ.Lisa@epa.gov>
> Subject: Perchlorate briefing
>
> Sam,
> I just had a conversation with Eric. He said the meeting with with Dave Ross and the Administrator has been delayed however he said we need to put together the briefing materials ASAP. He gave me a brief summary of the 3 options to reflect based on direction from last week. I can email you those point but thought you might have in your notes. He had one addition that is for the option recommending a MCL we should specify that value would be 18. Have you been working on preparing materials? Eric was hoping to have them by tomorrow for his review. Please let me know. I'm out of the office for an appt. but will follow up via email shortly.
>
> Lisa
> <Option Selection for Perchlorate 11-12-19 v1.docx>

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 4/30/2020 6:52:38 PM
To: Flowers, Lynn [Flowers.Lynn@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
Subject: RE: question about perchlorate FAR
Attachments: DRAFT Perchlorate Action Memo 4-13-2020.docx

Hi Lynn,
We don't have a cleared fact sheet, but the attached **draft** action memo has some talking points that may be helpful.

Lisa

From: Flowers, Lynn <Flowers.Lynn@epa.gov>
Sent: Thursday, April 30, 2020 2:21 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: question about perchlorate FAR

Hi! Do you have a one-pager you could share on the facts in the FRN that we could work from? That would be so helpful if possible.
Also – we are thinking about that health advisory issue and the IRIS RfD here in ORD. Maybe we can talk about what you think sometime before the FAR meeting?
Thanks---
Lynn

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Advisor, Policy and Engagement
Office of Research and Development
USEPA, Washington, DC
(ph)202-564-6293, (cell)202-834-8393

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 11/13/2019 5:32:17 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: Revised briefing document - Perchlorate
Attachments: Option Selection for Perchlorate 11-12-19 v1.docx

Hi Eric,

Attached is a revised version of the briefing document, based on Jennifer's direction and comments during last week's meeting. Lisa reviewed this version and provided additional edits. I left two placeholders in this document for the input from OLEM as well as from OGC.

I sent this draft version to Karyn and she is working on providing OGC's input to us. Let me know if you have comments or any suggested edits.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 4/29/2020 4:18:47 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: Draft Perchlorate Response to Comment Document
Attachments: Consolidated Perchlorate Draft Comment Response Document 4-29-20.docx; Comment response ID.docx

Flag: Follow up

Hi Eric,
Please see the attached draft response to comment document for the perchlorate proposal. There are comment bubbles in this version, but you can review in "no markup" if you'd prefer. I've also attached a key I used as a cross reference comments since some responses point to others. This is in my short had so may not be as useful for you. Let us know if you have questions or concerns.
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, April 29, 2020 1:43 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Draft Perchlorate Response to Comment Document

Hi Lisa,

Attached is the draft Perchlorate RtC Document. I incorporated the final input provided by ORD. This version also includes annotated comments from reviewers. Let me know if we should also provide a clean copy for review at this stage.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Comment response ID

#1.1	Agree with EPA withdraw & EPA withdraw rationale
#1.7	Disagree with EPA withdraw & EPA withdraw rationale
#1.16	Withdraw will not stop superfund clean up
#2.1	Support MCL 56
#2.6	support lower than 56
#3.1	Support 18
#4.1	Support lower than 18
Page 5-1	SDWA legal authority to withdraw a reg det
#5.1	MCLG is protective with adequate margin of safety
#5.2	Withdraw allowed under the CD
#6.1	UCMR update for CA and MA
#6.7	Use of hypochlorite
#7.1	Update of HA
#8.5	Selection of studies
#8.6	Korevaar reanalysis
#8.7	Derivation of MCLG/protective of sensitive life stage
#8.9	Population based approach
#8.11	SAB=PBPK not RfD
#8.32	1, 2, 3 IQ is policy decision
#8.59	BBDR model has lack of transparency
#8.71	UF according to EPA guidance, UF=3 appropriate
#8.73	SAB recommendation for BBDR model
#8.78	RSC for food, peer review
#8.80	RSC for food not a factor in BBDR model
#8.95	Korevaar reanalysis is transparent
#8.106	Rationale for UF in TSD
#8.113	UF_D not needed for deficiencies in the perchlorate database
#10.4	EPA should provide technical assistance
#10.5	Significant burden of NPDWR

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 4/3/2020 1:08:33 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN
Attachments: Draft Perchlorate Reg Det Withdrawal FR Notice 4-2-20 v1 Clean.docx; Draft Perchlorate Reg Det Withdrawal FR Notice 4-2-20 v1 Redline.docx; Perchlorate Action Memo 4-2-20.docx; Transmittal Memo EB to JM 4-2-20.docx; Transmittal Memo JM to DR 4-2-20.docx

Hi Eric,
I'm not sure why Sam sent these to you as I have not yet seen how edits were handled. I would like to review to make sure we've addressed all comments. I'll send revised documents Monday. Okay?

Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Thursday, April 02, 2020 5:31 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN

Hi Eric

We have incorporated most of your edits as well as the new items discussed during our meeting on Tuesday. There are a few edits that were not adopted following feedback received from OGC, specifically OGL-WLO

Ex. 5 AC/AWP/DP

As discussed with OGC earlier this week they will wait for Jennifer's feedback to look at the document again, but I will wait to see if you any additional feedback on this version to send Pooja and Carrie a courtesy copy concurrently when the document is transmitted to Jenifer.

In addition, here you will see the memos that the team prepared for transmitting the package up the review/concurrence chain. Please let me know if you have further comments or any questions regarding the attached documents.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Saturday, March 28, 2020 11:08 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN

Sam:
Thank you for preparing the draft final action for perchlorate. I have reviewed the document and have a number of edits and comments in the attached. Please let me know if you would like to arrange a meeting to discuss my comments.
Thank you again for the work you and the team have done in these challenging conditions.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, March 20, 2020 2:00 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Draft - Perchlorate Reg Det Withdrawal FRN

Hi Eric,

Attached you will find the draft FRN announcing the withdrawal of the Reg Det for perchlorate. Lisa already reviewed an earlier version of this notice and we have incorporated the requested edits. We also sent this version of the FRN to OGC for their review and feedback.

We will work on incorporating your comments and input concurrently with any input we get from OGC.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/2/2020 9:31:09 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Newcamp, Caitlin [Newcamp.Caitlin@epa.gov]; Alattar, Zaineb [alattar.zaineb@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN
Attachments: Draft Perchlorate Reg Det Withdrawal FR Notice 4-2-20 v1 Clean.docx; Draft Perchlorate Reg Det Withdrawal FR Notice 4-2-20 v1 Redline.docx; Perchlorate Action Memo 4-2-20.docx; Transmittal Memo EB to JM 4-2-20.docx; Transmittal Memo JM to DR 4-2-20.docx

Hi Eric

We have incorporated most of your edits as well as the new items discussed during our meeting on Tuesday. There are a few edits that were not adopted following feedback received from OGC, specifically OGL-WLO

Ex. 5 AC/AWP/DP

As discussed with OGC earlier this week they will wait for Jennifer's feedback to look at the document again, but I will wait to see if you any additional feedback on this version to send Pooja and Carrie a courtesy copy concurrently when the document is transmitted to Jenifer.

In addition, here you will see the memos that the team prepared for transmitting the package up the review/concurrence chain. Please let me know if you have further comments or any questions regarding the attached documents.

Thank You
Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Saturday, March 28, 2020 11:08 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN

Sam:
Thank you for preparing the draft final action for perchlorate. I have reviewed the document and have a number of edits and comments in the attached. Please let me know if you would like to arrange a meeting to discuss my comments.

Thank you again for the work you and the team have done in these challenging conditions.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, March 20, 2020 2:00 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Draft - Perchlorate Reg Det Withdrawal FRN

Hi Eric,

Attached you will find the draft FRN announcing the withdrawal of the Reg Det for perchlorate. Lisa already reviewed an earlier version of this notice and we have incorporated the requested edits. We also sent this version of the FRN to OGC for their review and feedback.

We will work on incorporating your comments and input concurrently with any input we get from OGC.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 1/6/2020 6:34:50 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
CC: Huff, Lisa [Huff.Lisa@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Perchlorate briefing
Attachments: Option Selection for Perchlorate 1-6-20 v1 Redline.docx; Option Selection for Perchlorate 1-6-20 v1 Clean.docx

Hi Eric,

Here are two documents. 1) The revised clean version and 2) a redline version that includes responses to the previous comments. Let us know if you have any questions.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, January 06, 2020 9:13 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Cc: Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Thanks Sam
We need to have a revised version by 2:00 pm today at the latest. Let me know if that will not be possible.
Thanks
Eric

From: Hernandez-Quinones, Samuel
Sent: Monday, January 06, 2020 9:11 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Cc: Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric,

We have a version that Lisa sent on Friday. Rajiv is working on completing the requested population data on the table. I will work with Rajiv to try to address the comments provided to us. Let me know when are these edits needed for.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, January 06, 2020 9:05 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate briefing

Lisa Christ will not be in today. She was working to incorporate edits to address the attached comments on Friday. Do any of you have her revised version?
Thanks in advance.
Eric

From: Burneson, Eric
Sent: Friday, January 03, 2020 1:03 PM
To: Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Perchlorate briefing

Lisa:
I received comments from Jennifer on the perchlorate briefing and the attached reflects those comments. The most significant ask is to present the total population vs protected population breakdown as shown on page 4. Let me know if you have any concerns or if it is not possible to make the requested changes before noon on Monday. Thanks

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Khera, Rajiv [Khera.Rajiv@epa.gov]
Sent: 1/6/2020 3:47:20 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: Perchlorate briefing
Attachments: Option Selection for Perchlorate 12-20-19v4 rk.docx

Hi Sam-
Please see attached the revised perchlorate briefing with a table on page 4 containing population information and a few additional edits on pages 5-6. Thanks
Rajiv

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, January 06, 2020 9:18 AM
To: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Perchlorate briefing

Thanks you Rajiv.

Note that related to another Jennifer comment about the number of systems using hypochlorite, Lisa had found an JAWWA article from 2011 that stated roughly 1/3rd of water systems use Hypochlorite.

From: Khera, Rajiv
Sent: Monday, January 06, 2020 9:13 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric-
Per your request, I am working on the table (total pop vs protected pop) and will send it to you by 10am. I don't have Lisa's revised version. Thanks
Rajiv

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, January 06, 2020 9:05 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate briefing

Lisa Christ will not be in today. She was working to incorporate edits to address the attached comments on Friday. Do any of you have her revised version?
Thanks in advance.
Eric

From: Burneson, Eric
Sent: Friday, January 03, 2020 1:03 PM
To: Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Rodgers-Jenkins,

Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Perchlorate briefing

Lisa:
I received comments from Jennifer on the perchlorate briefing and the attached reflects those comments. The most significant ask is to present the total population vs protected population breakdown as shown on page 4. Let me know if you have any concerns or if it is not possible to make the requested changes before noon on Monday. Thanks

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 11/15/2019 7:07:20 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: RE: Perchlorate briefing
Attachments: Option Selection for Perchlorate 11-15-19 v1.docx

Hi Eric,

I have updated the briefing document after talking with Lisa Huff about the additional edits you wanted to see in the document.

I have also incorporated OGCs input into this version of the briefing document, which contains language about their legal strategy and the implications on the schedule. Let me know if you have any comments or if you would like us to include any additional information.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Thursday, November 14, 2019 4:32 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Re: Perchlorate briefing

Thanks Sam. Looks like you have the relevant points other than Eric said we should put as an option the MCLG if 18 not the other values. I'll talk to you in the morning and we can see what Eric wants to see.

Lisa

> On Nov 14, 2019, at 3:51 PM, Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov> wrote:
>
> Hi Lisa,
>
> I sent a revised draft version of the briefing document to Eric earlier this week. We are waiting for additional input that OGC will provide to us. Here is the revised document, as reviewed by Lisa, that I shared with Eric. If you have additional information, I will be glad to incorporate into the document.
>
> I will be in the office tomorrow morning if you want to hand those notes to me, or you can also email them.
>
> Thanks
> Sam
> ==========
> Samuel Hernández Quiñones, P.E.
> Environmental Engineer
> Office of Water
> Environmental Protection Agency
> 1200 Pennsylvania Ave. NW
> Washington, DC 20460
> 202-564-1735
>
> "USEPA Protecting Human Health and the Environment"
>
> -----Original Message-----
> From: Huff, Lisa <Huff.Lisa@epa.gov>
> Sent: Thursday, November 14, 2019 3:37 PM
> To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
> Cc: Christ, Lisa <Christ.Lisa@epa.gov>

> Subject: Perchlorate briefing
>
> Sam,
> I just had a conversation with Eric. He said the meeting with with Dave Ross and the Administrator has been delayed however he said we need to put together the briefing materials ASAP. He gave me a brief summary of the 3 options to reflect based on direction from last week. I can email you those point but thought you might have in your notes. He had one addition that is for the option recommending a MCL we should specify that value would be 18. Have you been working on preparing materials? Eric was hoping to have them by tomorrow for his review. Please let me know. I'm out of the office for an appt. but will follow up via email shortly.
>
> Lisa
> <Option Selection for Perchlorate 11-12-19 v1.docx>

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 11/21/2019 9:38:25 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: RE: Perchlorate briefing
Attachments: Option Selection for Perchlorate 11-21-19 v1.docx

Hi,

Here is the revised version of the briefing document which incorporates the latest suggested edits. I adjusted the OMB review timeframe from 90 to 75 days, so that we can still meet the consent decree deadline. Let me know if you have any comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Thursday, November 21, 2019 3:16 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Thank you Sam: A few comments in the attached and an assumption to use Dec 13 as the date of the Administrators briefing. Can you adjust the schedule and get this back to me?
Thanks
Eric

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Tuesday, November 19, 2019 9:43 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric,

I have incorporated your edits as well as the additional occurrence data provided by the Reg Det Team, and the new input from OGC.

Please take particular attention to the edits I made to the language you inserted in the "Rationale" section of Option 1. I made the edits considering the data provided by the Reg Det Team.

Let me know if you have any comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Burneson, Eric <Burneson.Eric@epa.gov>

Sent: Friday, November 15, 2019 2:16 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Sam I just sent you my comments on the previous version. Let me know if there are edits you made in your version that need to be incorporated into mine.

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Friday, November 15, 2019 2:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric,

I have updated the briefing document after talking with Lisa Huff about the additional edits you wanted to see in the document.

I have also incorporated OGCs input into this version of the briefing document, which contains language about their legal strategy and the implications on the schedule. Let me know if you have any comments or if you would like us to include any additional information.

Thanks
Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Thursday, November 14, 2019 4:32 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
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Thanks Sam. Looks like you have the relevant points other than Eric said we should put as an option the MCLG if 18 not the other values. I' ll talk to you in the morning and we can see what Eric wants to see.

Lisa

> On Nov 14, 2019, at 3:51 PM, Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov> wrote:
>
> Hi Lisa,
>
> I sent a revised draft version of the briefing document to Eric earlier this week. We are waiting for additional input that OGC will provide to us. Here is the revised document, as reviewed by Lisa, that I shared with Eric. If you have additional information, I will be glad to incorporate into the document.
>
> I will be in the office tomorrow morning if you want to hand those notes to me, or you can also email them.
>
> Thanks
> Sam
> ==========
> Samuel Hernández Quiñones, P.E.
> Environmental Engineer
> Office of Water
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> 1200 Pennsylvania Ave. NW
> Washington, DC 20460
> 202-564-1735
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> "USEPA Protecting Human Health and the Environment"
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> -----Original Message-----
> From: Huff, Lisa <Huff.Lisa@epa.gov>
> Sent: Thursday, November 14, 2019 3:37 PM
> To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
> Cc: Christ, Lisa <Christ.Lisa@epa.gov>

> Subject: Perchlorate briefing
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> Sam,
> I just had a conversation with Eric. He said the meeting with with Dave Ross and the Administrator has been delayed however he said we need to put together the briefing materials ASAP. He gave me a brief summary of the 3 options to reflect based on direction from last week. I can email you those point but thought you might have in your notes. He had one addition that is for the option recommending a MCL we should specify that value would be 18. Have you been working on preparing materials? Eric was hoping to have them by tomorrow for his review. Please let me know. I' m out of the office for an appt. but will follow up via email shortly.
>
> Lisa
> <Option Selection for Perchlorate 11-12-19 v1.docx>

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/18/2020 6:54:21 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: 2 perchlorate documents -- for your records
Attachments: Redline Perchlorate Reductions 2-18-20 v1.docx

Hi Eric,

Here is the revised redline version of the document. Let me know if you have additional comments or suggested edits.

If there are no additional edits required, please let me know and I will send you a clean version.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 18, 2020 11:19 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thank you Sam and Rajiv for your work to address my comments. I have a few more follow up request in the attached. Can you see if we can get OLEM to expedite their feedback on the table? Putting forward this document is critical to getting decisions needed to make the court filing.
Eric

From: Hernandez-Quinones, Samuel
Sent: Tuesday, February 18, 2020 10:23 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Hi Eric, please see attached document. It incorporates your suggested edits and addresses your questions.

I am also waiting for some additional feedback form OSWER on the table they provided, as they way it reads now it appears to show several entries for the same mitigation site. Depending on their feedback we might have to update that table.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Tuesday, February 18, 2020 10:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Yes I'll check with Sam and get back to you.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 18, 2020 10:07 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: 2 perchlorate documents -- for your records

Lisa:
I sent the attached comments to Lisa Christ on Thursday but I don't think I received a revised document. Since Lisa is out today, can you check with the Team to get me a revised today?
Thanks
Eric

From: Burneson, Eric
Sent: Thursday, February 13, 2020 2:05 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thank You Lisa
I have a few comments/edits on the perchlorate reduction document in the attached.
Eric

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: 2 perchlorate documents -- for your records

Eric – just wanted to put both documents in one place for you. Both have been reviewed by Jennifer and Christina. Lisa

---

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for**

perchlorate is available. It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Wadlington, Christina [Wadlington.Christina@epa.gov]
Sent: 5/23/2019 2:50:41 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Subject: RE: Draft Perchlorate Signature /Roll out schedule:
Attachments: PrePub Final Version NPDWR Proposed Perchlorate Rule-508.pdf; PrePub Final Version NPDWR Proposed Perchlorate Rule.docx

Here's the prepub 508/web version for your records.

From: Hernandez-Quinones, Samuel
Sent: Thursday, May 23, 2019 10:43 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>; Adams, Darryl <Adams.Darryl@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

Hi,

Attached is the Final Version for signature. Thank You for assisstance on this effort.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Thursday, May 23, 2019 10:34 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>; Adams, Darryl

<Adams.Darryl@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

All: We have just concluded discussions with OMB and they are opening ROCIS for clearance of the package (that I sent separately to Darryl to and Mary). Sam will send the clean versions forward for signature shortly. Thank you all for your continued focus on this issue and for helping us to achieve this goal.

From: Burneson, Eric
Sent: Wednesday, May 22, 2019 5:36 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; 'Joe Tiago (Tiago.Joseph@epa.gov)' <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <manibusan.mary@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

All:
I just had a conversation with OMB and they estimate that within the next hour they will be transmitting minor edits to the FRN and that are not substantive in nature. They also expect to let us know that they will be opening ROCIS at that time to receive the final version for close out of OMB review. They noted that there are some issues being raised by SBA that could impede that timeline but they expect those issues will be resolved.

I also learned that the A.O. is still anticipating signature by 10:00 am tomorrow.

Thanks for your continued work on this important project.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Monday, May 20, 2019 3:54 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; 'Joe Tiago (Tiago.Joseph@epa.gov)' <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <manibusan.mary@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

All:
Attached please find an updated timeline to reflect some adjustments based upon when OMB is available for discussion tomorrow. We have informed OMB our intended timeline for signature and they indicated that it was extremely

compressed and that they could not guarantee clearance in time but that they would do what they could to expedite completion of the interagency review. OMB has been forwarding the comments from other Federal Agencies today but we are still awaiting the OMB consolidated mark up.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Friday, May 17, 2019 12:39 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Joe Tiago (Tiago.Joseph@epa.gov) <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Draft Perchlorate Signature /Roll out schedule:

All: We have received notice that the already short time frame for signature for the perchlorate proposal needs to be shortened to assure signature before 1:00 pm on Thursday May 23. Attached please find a timeline of the actions that must take place between receipt of Inter Agency comments from OMB (expected COB on 5/20) and the new signature deadline we have been asked to work against. Can you please review the attached and let me know if there are significant steps that will require time not anticipated in the attached timeline.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

The EPA Administrator signed the following proposed rule on 5/23/2019, and EPA is submitting it for publication in the Federal Register (FR). While we have taken steps to ensure the accuracy of this Internet version of the proposed rule, it is not the official version of the proposed rule for purposes of public comment. Please refer to the official version in a forthcoming FR publication, which will appear on the Government Printing Office's FDsys website (https://www.gpo.gov/fdsys/). It will also appear on Regulations.gov (https://www.regulations.gov/) in Docket No. EPA-HQ-OW-2019-0780.

Once the official version of this document is published in the FR, this version will be removed from the Internet and replaced with a link to the official version

6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about

perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, the EPA is requesting comment on three alternatives: 1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18 µg/L), 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 µg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011, determination to regulate perchlorate in drinking water based on new information that indicates that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and there may not be a meaningful opportunity for health risk reduction through a drinking water regulation. Under this last alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at [HYPERLINK "http://www.regulations.gov"]. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit [HYPERLINK "http://www2.epa.gov/dockets/commenting-epa-dockets"].

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This proposed rule is organized as follows:

I. General Information

A. What is the EPA Proposing?

ED_005043_00060973-00003

B. Does This Action Apply to Me?

II. Background

A. What is Perchlorate?

B. Statutory Authority

C. Statutory Framework and Regulatory History

III. Assessment and Modeling of the Health Effects of Perchlorate

A. 2008 Preliminary Regulatory Determinations

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

C. Science Advisory Board Recommendations

D. Perchlorate Model Development and Peer Reviews

E. Sensitive Population for Deriving MCLG

F. BBDR Model Specification for the Sensitive Population

G. Epidemiological Literature

H. Identifying a Point of Departure for Developing the MCLG

I. Translate PODs to RfDs

J. Translate RfD into an MCLG

IV. Maximum Contaminant Level Goal and Alternatives

V. Maximum Contaminant Level and Alternatives

VI. Occurrence

VII. Analytical Methods

VIII. Monitoring and Compliance Requirements

A. What are the Monitoring Requirements?

B. Can States Grant Monitoring Waivers?

C. How are System MCL Violations Determined?

D. When Must Systems Complete Initial Monitoring?

E. Can Systems Use Grandfathered Data to Satisfy the Initial Monitoring Requirement?

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

B. What are the Public Notification Requirements?

X. Treatment Technologies

A. What are the Best Available Technologies?

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XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

B. What are the State Record Keeping Requirements?

C. What are the State Reporting Requirements?

XII. Health Risk Reduction Cost Analysis

A. Identifying Affected Entities

B. Method for Estimating Costs

C. Method for Estimating Benefits

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D. Comparison of Costs and Benefits

XIII. Uncertainty Analysis

A. Uncertainties in the MCLG Derivation

B. Uncertainties in the Economic Analysis

XIV. Request for Comment on Proposed Rule

XV. Request for Comment on Potential Regulatory Determination Withdrawal

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

C. Paperwork Reduction Act

D. Regulatory Flexibility Act (RFA)

E. Unfunded Mandates Reform Act

F. Executive Order 13132: Federalism

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use

J. National Technology Transfer and Advancement Act of 1995

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of 56 µg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 µg/L.

The EPA is proposing an NPDWR for perchlorate in accordance with its February 11, 2011, (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such

contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is soliciting comment on two alternative MCLG/MCL values of 18 µg/L and 90 µg/L respectively. Third, in light of new considerations that have come to the EPA's attention since it issued its positive regulatory determination in 2011, including information on lower levels of occurrence of perchlorate than the EPA had previously believed to exist and new analysis of the concentration that represents a level of health concern, this action also discusses and requests comment on an alternative action under which the EPA would withdraw its 2011 determination to regulate perchlorate. Under this alternative, there would be no MCLG or NPDWR for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems
State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If

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you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Statutory Framework and Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water system. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems (CWS) and non-

transient, non-community water systems (NTNCWS). The UCMR collects data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556) which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999, 2000b).

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule knows as the sodium/iodide symporter (NIS), which may lead to decreases in two hormones, thyroxine (T3) and triiodothyronine (T4) and increases in thyroid-stimulating hormone (TSH) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington,

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the recommended National Research Council RfD of 0.7 μg/kg/day for perchlorate. The reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA,

2008a)","plainCitation":"(USEPA,

2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal

Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that

they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Based primarily on the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In January 2009 the EPA published an interim health advisory for perchlorate of 15 µg/L, consistent with the HRL derivation for perchlorate of 15 µg/L described above. Health Advisories are non-enforceable and non-regulatory and provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health Advisories provide the public, including the most sensitive populations, with a margin of protection from a lifetime of exposure. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children.

The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (74 FR 41883; USEPA, 2009a). After careful consideration of public comments on the October 2008 and August 2009 notices, on February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011a). The Agency stated then that when considering the alternative HRL benchmarks described in the 2009 notice, the likelihood of perchlorate to occur at levels of concern had significantly increased in comparison to the levels described on the 2008 preliminary negative determination. The EPA concluded that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally described in the 2008 notice.

In its 2011 determination, the Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data did not comply with data quality guidelines and were not representative of current conditions. In response to this

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request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data for systems in California and Massachusetts using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than October 31, 2018, and finalize an NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water was later extended to May 28, 2019. The consent decree is available in the docket for today's proposed rule.

III. Assessment and Modeling of the Health Effects of Perchlorate

Perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the NIS (ATSDR, 2008; Greer et al., 2002; NRC, 2005; SAB 2013; Taylor et al., 2013). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB for the U.S. EPA, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB for the U.S. EPA, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang

et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

The mode of action of perchlorate toxicity has been proposed as follows: exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland through the NIS (NRC, 2005; SAB for the U.S. EPA, 2013). A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that T3 and T4 require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased TSH, the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"eF6zWm7L","properties":{"formattedCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","plainCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","noteIndex":0},"citationItems":[{"id":428,"uris":["http://zotero.org/groups/945096/items/UIANA947"],"uri":["http://zotero.org/groups/945096/items/UIANA947"],"itemData":{"id":428,"type":"bill","title":"Toxicological Profile for

Perchlorates","author":[{"family":"ATSDR","given":""}],"issued":{"date-parts":[["2008"]]}},{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid tormone levels in adolescent and adult men and women living in the United States","container-title":"Environmental Health Perspectives","page":"1865-1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]}},{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the national health and nutrition examination survey 2007-8","container-title":"Environmental

research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors ...","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID: 23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]}}},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy,

including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L. Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to

perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to decrements in neurocognitive function in offspring (Alexander et al., 2017; Thompson et al.,

[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

2018; Wang et al., 2016). There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate's mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in sensitive populations. Therefore, based on the known mode of action of perchlorate the Agency estimated potential health risks using a novel approach suggested by the EPA's Science Advisory Board (SAB for the U.S. EPA, 2013). The EPA's approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency,

decreased synthesis of T3 and T4, and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency). Based on these findings, the NRC recommended a reference dose of 0.7 µg/kg/day.

Based on NRC's analysis, the EPA established a perchlorate reference dose (RfD) of 0.7 µg/kg/day in 2005 (USEPA, 2005). This value was based on a no observed effect level (NOEL) of 7 µg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

As discussed above, in 2008, the EPA derived an HRL of 15 µg/L using the RfD of 0.7 µg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (i.e., food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the subpopulation identified by the NAS as likely the most sensitive to the effects of perchlorate exposure, fetuses.

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the

EPA developed alternative HRLs for other sensitive populations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 μg/L to 47 μg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon

perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;

- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically free T4 (fT4)) that are associated with maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Reviews

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, i.e., breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). In addition to estimating effects on breast fed infants, several reviewers recommended that the EPA shift the primary focus of its analysis to modeling the exposure implications to the fetus during early pregnancy. This was based on the knowledge that fetuses lack a functioning thyroid gland until approximately 16 gestational weeks and the substantial epidemiological evidence linking early pregnancy low fT4 levels with adverse neurodevelopmental outcomes [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. Specifically, the SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: "the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" (SAB for the U.S. EPA, 2013, p. 19).

The EPA considered all recommendations from the 2017 peer review. The previously developed BBDR model describing perchlorate's effects in the third trimester (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b) was calibrated only for that phase of pregnancy, not for the first trimester, and lacked a description of TSH signaling (feedback) that becomes significant as individuals become hypothyroxinemic or hypothyroid. In particular, this signaling was considered necessary to accurately predict responses of women with very low iodine intake,

which was also part of the 2017 peer review recommendations. Therefore, the Lumen et al., (2009b) model needed to be revised to address these recommendations and the EPA implemented those changes needed to increase the scientific rigor of the model and modeling results. These modifications include:

- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in January 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches in the draft *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (MCLG Approaches Report) to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018). The 2018 peer review identified a variety of strengths and limitations of the modeling (to be discussed in more detail later in this notice). The peer review panel was largely supportive of the efforts described in the MCLG Approaches Report, as evidenced by the following from the peer review final report:

Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).

The EPA also presented an alternative, population-based approach evaluating the shift in the proportion of the population that would fall below a hypothyroxinemic cut point, given exposure to perchlorate (Section 7 of the MCLG Approaches Report). This approach does not directly connect the BBDR output to a neurodevelopmental endpoint. However, for pregnant women in early pregnancy, this shift could be related to avoiding an increase in the population of offspring's risk of adverse neurodevelopmental impacts. The 2018 peer review identified strengths associated with this approach, including

1) the central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; 2) this approach encompasses a variety of adverse neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and 3) this approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an

adverse neurodevelopmental effect. (External Peer Reviewers for U.S. EPA, 2018, p. 7)

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for an MCLG based on this approach to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The peer-review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. The EPA is requesting public comment in Section XIV on the adequacies and uncertainties of the methodology to derive the MCLG including the decision not to pursue this population-based approach for setting the MCLG.

Based on the comments of the peer reviewers, the EPA's final analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed

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to perchlorate in drinking water (see Figure 1). In summary, because of the known mode of action, the lack of epidemiological studies particularly in the sensitive populations and the direction of the SAB to use a "data-driven approach [which] represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages" (p. 2, SAB 2013 for U.S. EPA), the EPA uses a combination of the BBDR model that simulates perchlorate potential impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail, highlighting each step in which decisions and assumptions were made.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring

[EMBED Visio.Drawing.15]

Note: Process figure does not imply the strength of scientific evidence.

E. Sensitive Population for Deriving MCLG

SDWA 1412(b)(4)(A) requires MCLGs to be set at a concentration in water "at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." SDWA 1412(b)(3)(C)(V) further requires that the EPA "consider the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." The EPA has interpreted these requirements to establish MCLGs that avoid adverse effects within the

portions of the population that are at greater risk of adverse effects from exposure to the contaminant. The EPA is proposing an MCLG that is developed to protect the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of an fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The choice of this population is consistent with discussion by the NRC (2005), and the SAB (2013). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-number>246</rec-number><foreign-keys><key app="EN" db-

id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 μg/day). Assuming 2 or 4 μg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 μg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than

[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

75 μg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there are reports in the scientific literature suggesting that minor perturbations in thyroid hormone levels in the first trimester mother may adversely impact her offspring's neurodevelopment. Specifically, some studies show that children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) have a higher risk of reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Notably these effects are correlated with both degree [ADDIN EN.CITE ADDIN EN.CITE.DATA] and duration [ADDIN EN.CITE <EndNote><Cite><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(Pop et al., 2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-

title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] of maternal hypothyroxinemia [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>`; p. 10</Suffix><DisplayText>(SAB, 2013; p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. This finding is consistent with conclusions by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><Prefix>CalEPA`,

</Prefix><Suffix>`; p. 90</Suffix><DisplayText>(CalEPA, 2015; p. 90)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency (CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

Specifically, two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. [HYPERLINK \l "_ENREF_9" \o "Costeira, 2011 #7"] found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, [HYPERLINK \l "_ENREF_17" \o "Henrichs, 2010 #928"] found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the

relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB for the U.S. EPA, 2013). Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive lifestage and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

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The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and
- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to many other PBPK models. Because perchlorate does not undergo metabolism in vivo (Clewell et al., 2007), potential uncertainty from this factor of the model is avoided since it does not need to be described.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model estimates serum thyroid hormone levels in the mother at specific gestational weeks, given specific levels of iodine intake, the TSH feedback loop strength, and

perchlorate doses. As noted above, to be health protective the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG, thereby protecting both this target sensitive population with an adequate margin of safety and those who are less sensitive with an even larger margin of safety.

The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al., (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>1160</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-number>1160</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206437">1160</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce,</author><author>Braverman</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice and

Research: Clinical Endocrinology and Metabolism</secondary-title><alt-title>Best Pract Res Clin Endocrinol Metab</alt-title><short-title>Best Practice and Research: Clinical Endocrinology and Metabolism</short-title></titles><alt-periodical><full-title>Best Pract Res Clin Endocrinol Metab</full-title></alt-periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn>ISSN 1521-690X
EISSN 1532-1908</isbn><label>755955</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1016/j.beem.2009.08.009</url></related-urls></urls><electronic-resource-num>10.1016/j.beem.2009.08.009</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The EPA selected an iodine intake level of 75 µg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 µg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH

[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(

Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><Pages>332</Pages><DisplayText>(Alexander et al., 2017, p. 332)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American journal of obstetrics and gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-title></periodical><pages>62-e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

ranges between 4.51 and 5.41 milli-international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones[ADDIN EN.CITE ADDIN EN.CITE.DATA]. The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in [REF _Ref517525852 \h * MERGEFORMAT].

Table III-[SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 Levels: Pregnant Women at Gestational Week 13, Assuming Low (75 µg/day) Iodine Intake and with Muted TSH feedback strength[a][]

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)
5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] pTSH = 0.398; see USEPA, (2018b) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67. All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestation week and did not account for variation in perchlorate and iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (e.g. Blount et al., 2007) and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3). The EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4 for the identified sensitive population, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based

on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4 concentrations for women with low fT4 of childbearing age would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. To protect the most sensitive population from adverse effects, the EPA chose to use the 10th percentile from this distribution of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population[5].

G. Epidemiological Literature

The SAB recommended that the EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010;

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Roman et al., 2013; van Mil et al., 2012). These individual studies showing that maternal hypothyroxinemia is associated with offspring neurodevelopment are also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Additionally, the American Thyroid Association concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

The EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes given: 1) the body of scientific literature regarding this association, and 2) the SAB recommendation that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25). Instead, the EPA conducted a "methodologic approach to reviewing the literature" to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. More specifically, the EPA only used studies that had sufficient data to show a quantitative relationship between maternal fT4 and a neurodevelopmental

outcome. The EPA acknowledges that by not giving any weight to the studies that did not show a quantitative relationship between fT4 and neurodevelopmental outcomes, the Agency may be overestimating the dose of perchlorate that may be associated with adverse neurodevelopmental outcomes. This is a health protective decision that adds to the margin of safety.

Ultimately, the EPA developed a dose-response function that estimates incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

The specifics of this "methodologic approach to reviewing the literature" follow. First, the EPA identified and screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- compatible with the sensitive life stages identified by the NRC and SAB;
- continuous measure of thyroid hormone values (versus categorical values);
- low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- access to underlying data.

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Second, using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40 studies). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia. Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition,

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[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

behavior and other outcomes. The EPA notes that by selecting the papers that potentially had dose response data the Agency is deviating from the systematic weight of evidence review approach to identify those studies that the SAB recommended we examine to derive the MCLG.

Third, from these 15 papers five were selected for dose response assessment - four related to cognition[ADDIN EN.CITE ADDIN EN.CITE.DATA] and one related to behavior [ADDIN EN.CITE

<EndNote><Cite><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(Endendijk, Wijnen, Pop, & van Baar, 2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk, J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar, A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories during pregnancy and child behavioral problems</title><secondary-title>Horm Behav</secondary-title></titles><periodical><full-title>Horm Behav</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was

being conducted, lack of all the data needed to complete a dose-response assessment (e.g., dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al., (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

As laid out for the peer reviewers, for each study that met the criteria identified above for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018b). These relationships were either presented in the original published paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to assure consideration of the populations likely to be at greater risk from the dose of perchlorate associated with a given change in fT4.

Table III-2 provides a summary of the changes in fT4 predicted to produce a 1, 2, and 3 percent decrease in any given neurodevelopmental effect and corresponding perchlorate doses. The choice of 1, 2, and 3% is based on the analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI). Specifically, a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points) equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively (Endendijk et al., 2017; Finken et al., 2013).

These results provide the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (derived from the epidemiologic literature[7]).

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[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the MCLG Approaches Report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

Table III-2. Estimated Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopment for the Population of Low-Iodine Intake Women of Reproductive Age Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al., (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1
Korevaar et al., (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8
Pop et al., (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al., (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al., (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al., (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al., (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

H. Identifying a Point of Departure for Developing the MCLG

From the seven analyses presented in Table III-2 above, the EPA chose to use its independent analysis of the Korevaar et al., (2016) data (comprising of 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. There are three reasons for this selection: 1) there is sufficient quantitative data to derive a health impact function for the sensitive population of interest; 2) the analysis adjusts for an appropriate set of confounders, and 3) the neurodevelopmental endpoint – intelligence quotient (IQ) – is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below). The other studies presented in Table III-2 do not provide one or more of these features (USEPA, 2018b).

The five identified papers evaluated a variety of endpoints with Korevaar et al., (2016) evaluating IQ, Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) using the Bayley Scale to evaluate PDI and MDI, Finken, van Eijsden, Loomans, Vrijkotte, and Rotteveel (2013) evaluating the SD of reaction time, and Endendijk, Wijnen, Pop, and van Baar (2017) evaluating anxiety/depression scores using the Child Behavioral Check List (CBCL). The SD of reaction time from Finken et al., (2013) was not well-received by the peer reviewers (External Peer Review for U.S. EPA, 2018) because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al., (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al., (2017) nor the Finken et al., (2013) analyses had functions for the sensitive life stage (i.e., their analyses were based on the full range of fT4 levels and did not concentrate on the impacts of low-end fT4 levels). For these reasons, the Endendijk et al., (2017) and Finken et al., (2013) papers were not selected for further evaluation.

The Korevaar et al., (2016) original and independent analyses are preferable compared to the Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) studies because neither function derived from the Pop et al., studies was adjusted for confounders. Additionally, both

Pop et al., papers have an N < 50 compared to the Korevaar et al., analyses, which have an N of greater than 3,600.[8]

Although the original Korevaar et al., (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al., (2016) EPA reanalysis was chosen over the original analysis because it included modifications to the analysis at the suggestion of the peer review panel. The revised analysis controls for a more parsimonious set of confounders (e.g., previously included variables such as infant gender, maternal parity, birthweight, mother's body mass index (BMI), and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al., (2016) model because of the feedback received during the peer review of the MCLG Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

> *Korevaar et al., [2016] controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of*

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[8] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609 due to the exclusion of subjects with imputed values for maternal fT4.

the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al., (2016) data, and making decisions about data quality and influential data points in the analysis. That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values. Subsequently, the EPA selected the Korevaar et al., (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ [9].

As indicated above, the EPA has utilized a health protective approach to this analysis consistent with the SDWA definition of the MCLG. The peer reviewers commented that this approach was fit-for-purpose. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and

[9] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the MCLG Approaches Report.

neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. As explained earlier, the results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior, and other outcomes such as autism. Among these studies, only 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous

variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al., (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al., (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek et al., 2017; Roman et al., 2013;

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Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al., (2011) and Gyllenberg et al., (2016). Although Endendijk et al., (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al., (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al., (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al., (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking.

Not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The

relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. Therefore, the EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data. In an attempt to minimize uncertainty, the EPA reanalyzed the data collected by Korevaar et al., (2016) using a spline function that estimates a coefficient specifically for the low range of the fT4 data.

There are a variety of neurodevelopmental endpoints used to examine behavior and cognition in children (e.g., intelligence quotient (IQ), motor skills, vocabulary and language development, stimulus responsiveness, etc.). The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al., (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. As such, in the derivation of the MCLG, IQ is a surrogate for a suite of potential neurodevelopmental effects that might occur to the offspring of hypothyroxinemic and iodine deficient mothers.

There are several different tests that are widely used to measure IQ in children, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean

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score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

Associations have been found between IQ scores and both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al., (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). Research suggests that children's rearing environment, including parental education, while growing up may increase IQ scores in adolescence by several points (e.g., Kendler et al., 2015).

IQ scores have been used to help diagnose disorders such as intellectual disability and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) IQ

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scores are used in an individual's comprehensive assessment to determine intellectual disability, which pairs standardized testing of intelligence with a clinical assessment of adaptive functioning. Intellectual disability is considered for individuals with an IQ score of about 70 or below (American Psychiatric Association, 2013).

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 percent extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint. Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, USEPA, 2012).

For the specific context of setting an MCLG for perchlorate, the EPA made a policy decision to evaluate the level of perchlorate in water associated with a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points). The EPA selected IQ as a surrogate for neurodevelopmental effects based upon its evaluation of the epidemiologic literature describe above. The need to utilize the best available

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peer reviewed data to inform scientific assumptions and policy choices to meet the statutory requirements associated with developing an MCLG under the SDWA highlights the challenges associated with regulating chemicals for which potential effects are indirect, and scientific data do not address all uncertainties. The Agency must make a policy decision informed by science, consistent with statutory requirements even in situations where the data do not provide clear choices. To develop the proposed MCLG for perchlorate, the EPA made a policy decision to use a 2 IQ point decrement in the population-distribution of IQ for the sensitive population. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants for which there is concern about potential thyroid effects, either under the SDWA or other statutory frameworks.

Applying these response rates to the results from the reanalysis of Korevaar et al., (2016), results in a POD dose of 3.1 μg/kg/day for a 1 point decrease in the sensitive population's IQ, a POD dose of 6.7 μg/kg/day for a 2 point decrease in the sensitive population's IQ, and a POD dose of 10.8 μg/kg/day for a 3 point decrease in the sensitive population's IQ. These PODs associated with a 1, 2, or 3 point decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the POD is designed to provide an adequate margin of safety for the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 μg/day and a TSH feedback loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the

methodological reasons described previously, the EPA believes that the selection of these parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive population and allows for an adequate margin of safety.

I. Translate PODs to RfDs

When deriving an RfD the EPA evaluates whether to apply uncertainty/variability factors to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002). As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a no-observed-adverse-effect-level (NOAEL), and an incomplete database. The factors are intended to account for: 1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); 2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); 3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); 4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and 5) uncertainty associated with extrapolation when the database is incomplete. (U.S. EPA, 2011b) The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., uncertainty factor (UF) for within-

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human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. The approach taken to derive the RfD attempts to address variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.

Further, as discussed in section III.C. of this notice the EPA believes that protecting the

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[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the MCLG Approaches Report.

fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. In addition, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is potentially because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et al., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the fetal thyroid begins secreting thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels available to the fetus. Given that the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. Therefore, as described above, the EPA selected an intraspecies UF of 3 to account for the uncertainties in

modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children.

The EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. As noted above, the Agency has opted to apply a UF of 3 to the POD, which adds an adequate margin of safety to the MCLG derivation. Section 4.4.5.3 (p 4-42) of *A Review of the RfD & RfC Processes* recommends reducing the intraspecies UF from a default of 10 "only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)" (p. xviii, USEPA, 2002).The EPA selected a UF of 3 instead of the full 10 because the modeled groups within the population that are identified as likely to be at greater risk to perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother) and has selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake).

Below we list the other uncertainty factors added and the justification.

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.

- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.
- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.
- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).
- The product of all the uncertainty factors (UF_H) is 3 (3 x 1 x 1 x 1 x 1).

Below we generate RfD's for each of the points of departure.

Using the POD of 6.7 µg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.2\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 µg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.0\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

J. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\ \left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 µg/kg/day for a 1 percent decrease in IQ, 2.23 µg/kg/day for a 2 percent decrease in IQ, or 3.6 µg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_W = relative source contribution of drinking water to overall perchlorate exposure.

To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate specific to women of childbearing age (i.e., non-pregnant, non-lactating, 15–44 years of age (0.032 L/kg/day). This decision is consistent with the analysis used in deriving an RSC, which was performed using food consumption information for a population of women of childbearing age from NHANES. The 90th percentile is chosen to account for variability in drinking water ingestion rates, but also adds another layer of health protection for 90% of women (Table III-3).

The EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable. The use of the drinking water intake for 15-44 year old women is consistent with the analysis used in deriving an RSC_W (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the

EPA's Exposure Factors Handbook (USEPA, 2011c) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis.

Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2019c). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in about 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (μg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The details of these assumptions are explained on page 5-5 of the Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (USEPA 2019c). Specifically, the EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the 20 samples included in the TDS data. In order to estimate the 95th percentile from the 20 samples, the EPA used the second-

highest test result for each food to represent the 95th percentile concentration. While simple, this method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine [ADDIN EN.CITE <EndNote><Cite><Author>Carriquiry</Author><Year>2016</Year><RecNum>2008</RecNum><DisplayText>(Carriquiry et al., 2016)</DisplayText><record><rec-number>2008</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039524">2008</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carriquiry, A. L. </author><author>Spungen, J. H.</author><author>Murphy, S. P.</author><author>Pehrsson, P. R.</author><author>Dwyer, J. T.</author><author>Juan, W.</author><author>Wirtz, M. S. </author></authors></contributors><titles><title>Variation in the iodine concentrations of foods: considerations for dietary assessment</title><secondary-title>The American Journal of Clinical Nutrition</secondary-title></titles><periodical><full-title>The American Journal of Clinical Nutrition</full-title></periodical><pages>877S–887S</pages><volume>104</volume><number>Suppl 3</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. The aforementioned method for identifying the 95th percentile concentration of perchlorate from food was selected over other, more “statistically based” methods for estimating percentiles as it avoids the need to assume a distributional shape for the samples. The EPA determined that it was more reliable to assume the empirically derived distribution as the basis for selecting the 95th

percentile (i.e., assuming the distribution was equal to the distribution of samples collected in the TDS), as opposed to forcing a distributional shape, such as normal or log-normal, onto the data that may not necessarily be appropriate. With the chosen method, we can at least be sure that the distributional shape is appropriate for the data at hand, whereas by choosing the alternative that assumes a distributional shape, in many instances we would not even be certain of that. The EPA used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 µg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile perchlorate food concentrations in TDS. This assures

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that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

The EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III-5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using the EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.0	56%	0.032	18
2.2	80%	0.032	56
3.6	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss, 2-point IQ loss, or a 3-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the NPDWR. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 µg/L based on the rationale and methodology described in Section III above. The derivation of the proposed MCLG uses a point of departure based upon a two percent decrease in IQ for offspring of hypothyroxinemic women of child bearing age have with low iodine intake. The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the subpopulation of interest.

As described in Section III, the EPA has selected model parameters and other factors for the derivation of the MCLG that are health protective, including the focus on the most sensitive life stage. The EPA believes that the selection of the combination of protective parameters and

this point of departure assures no known or anticipated adverse effects on the health of the most sensitive subpopulation and allows for an adequate margin of safety. The EPA also acknowledges the uncertainties in the derivation of the proposed (and alternative) MCLGs. The EPA acknowledges in particular the challenge associated with selecting the decrement of IQ that represents an adverse effect at the population level and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement given the absence of robust human epidemiological data directly linking perchlorate exposure to IQ decrements. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2019b). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018c). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

Because the EPA is taking comment on alternative MCLG values of 18 µg/L and 90 µg/L the Agency evaluated the feasibility of setting an MCL at these levels. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this level under field conditions (USEPA 2018a, 2019b). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction

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benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA Section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The UCMR 1 is the primary source of occurrence data the EPA relied on to estimate the number of water systems (and associated population) expected to be exposed at levels of perchlorate which could potentially exceed the proposed and alternative MCL levels. Since UCMR 1 data was first used to inform the Agency actions on the 2008 preliminary regulatory determination and the 2011 final regulatory determination, the Agency has modified its analysis of the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions at some States that have enacted perchlorate regulations since the UCMR 1 data was collected. Despite these updates, the EPA continues to rely on the UCMR

1 data because they are the best available data collected in accordance with accepted methods from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants (USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to the EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 μg/L for perchlorate in the UCMR.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The

UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

In September of 2012, the EPA received a "Request for Correction" letter from the United States Chamber of Commerce regarding information and data (i.e., the occurrence of perchlorate in drinking water) used by the EPA in its 2011 determination to regulate perchlorate. The U.S. Chamber of Commerce letter stated that the EPA relied upon: 1) data that did not comply with data quality guidelines and 2) data that was not representative of current conditions.

In response[12] to the U.S. Chamber of Commerce, the EPA conducted a detailed assessment of the source water sample detections and determined that it was most appropriate to exclude the source water sample detections from the UCMR 1 perchlorate data set when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 perchlorate data set. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 perchlorate data set. As a result of the assessment, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the entry point to the distribution system. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections from 149 PWSs.

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[12] See the EPA response letter at https://www.epa.gov/sites/production/files/2017-08/documents/12004-response_0.pdf

Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

In response to the U.S. Chamber of Commerce request, the EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two states. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 μg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states are now required to keep perchlorate levels in drinking water below their state limits, which are lower than the proposed MCL and alternative MCLs. Therefore, the UCMR 1 sampling results from systems in these states do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. The notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

To update the occurrence data for systems sampled during UCMR 1 from the States of California and Massachusetts, the EPA identified all systems and corresponding entry points

which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

Out of the 540 detections previously described the EPA updated data for 321 detections (320 from California systems and 1 from a Massachusetts system). The convention used by the EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported compliance monitoring data, if more than one data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were the EPA could not find updated entry point data, then the original data from UCMR 1 for such entry point was kept.

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Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 µg/L	15	525	540
Sample measurements > 18 µg/L	1	16	17
Sample measurements > 56 µg/L	0	2	2
Sample measurements > 90 µg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 µg/L	8	328	336
Entry points at which measurements > 18 µg/L	1	16	17
Entry points at which measurements > 56 µg/L	0	2	2
Entry points at which measurements > 90 µg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 µg/L	8	141	149
Systems at which measurements > 18 µg/L	1	14	15
Systems at which measurements > 56 µg/L	0	2	2
Systems at which measurements > 90 µg/L	0	1	1

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UAoGFPZv","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The total row counts and counts of measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements > 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements > 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements > 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ChxDKgDr","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting level; at the entry point level, the exposed population is approximately 4.3 million people served

by 336 entry points. Because the uniform population distribution assumption may over or underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCLs. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"adhRbcXq","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In summary, the perchlorate occurrence information suggests that at an MCL of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. One of these two systems would exceed the alternative MCL of 90 µg/L. In addition, at an MCL of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is ''feasible'', the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, the

SDWA directs the EPA to determine that it is economically and technologically feasible to ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain ''criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels.'' (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report (USEPA, 2019b).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of

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sample analysis and data reporting. All of the proposed EPA analytical methods provide performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

The EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework set out in 40 CFR 141 Subpart C (Standardized Monitoring Framework). Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. The EPA is proposing that consistent with the standardized monitoring framework water systems would be initially required to monitor quarterly for perchlorate. The EPA is also proposing that based upon the monitoring results States would be able to reduce the monitoring frequency to annually, once every three years or once every nine years if the State concludes that the system is reliably and consistently below the MCL. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point in the next quarter after the violation occurred (40 CFR 141.23(c)(7)). The state may allow the system to return to the reduced monitoring frequency when the state determines that the system is reliably and consistently below the MCL. However, the state cannot make a determination that

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the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples below the MCL have been collected (40 CFR 141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the state (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under this proposal, water systems may apply to the state, and states may grant, a 9-year monitoring waiver for perchlorate if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A state may grant a waiver for surface water systems after three rounds of annual monitoring with results less than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

Under this proposal, violations of the perchlorate MCL would be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the perchlorate MCL would be determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

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D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than 10,000 persons must collect 4 quarterly samples for perchlorate during the second compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the Standardized Monitoring Framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the third compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the Standardized Monitoring Framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered perchlorate data collected after January 1, 2020, to satisfy the initial monitoring requirements. To satisfy initial perchlorate monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for CWSs serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for NTNCWs and for CWSs serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

A community water system must prepare and deliver to its customers an annual Consumer Confidence Report (CCR) in accordance with requirements in 40 CFR 141 Subpart O.

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A CCR provides customers with information about their local drinking water quality as well as information regarding the water system compliance with drinking water regulations. Under this proposal CWSs would be required to report perchlorate information in their CCR.

B. What are the Public Notification Requirements?

All public water systems must give the public notice for all violations of NPDWRs and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, per 40 CFR 141.202(b)(1), notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation under this proposal.

X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by states to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other

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means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in states issuing small system variances under Section 1412(e) of the SDWA.

The Agency solicits public comment on the choice of available treatment technologies discussed in this section.

A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new

well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"s9dVZckb","properties":{"formattedCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","plainCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","noteIndex":0},"citationItems":[{"id":1048,"uris":["http://zotero.org/groups/945096/items/KIPNEQUM"],"uri":["http://zotero.org/groups/945096/items/KIPNEQUM"],"itemData":{"id":1048,"type":"paper-conference","title":"Castaic Lake Water Agency Operating Experience with Lead-Lag Anion Exchange for Perchlorate Removal","container-title":"Proceedings of the American Water Works Association Water Quality Technology Conference","event":"Water Quality Technology

Conference","author":[{"family":"Drago","given":"J.A."},{"family":"Leserman","given":"J.R."}],"issued":{"date-parts":[["2011",11]]}}},{"id":1154,"uris":["http://zotero.org/groups/945096/items/2DBS6UYD"],"uri":["http://zotero.org/groups/945096/items/2DBS6UYD"],"itemData":{"id":1154,"type":"article","title":"News: Ion=Exchange System Removes Perchlorate","publisher":"Membrane Technology","author":[{"literal":"Membrane Technology"}],"issued":{"date-parts":[["2006",4]]}}},{"id":1125,"uris":["http://zotero.org/groups/945096/items/6WYYWFY2"],"uri":["http://zotero.org/groups/945096/items/6WYYWFY2"],"itemData":{"id":1125,"type":"report","title":"Case Study: Municipality in the State of Massachusetts","author":[{"literal":"Siemens Water Technologies"}],"issued":{"date-parts":[["2009"]]}}},{"id":1118,"uris":["http://zotero.org/groups/945096/items/5PV8GPIA"],"uri":["http://zotero.org/groups/945096/items/5PV8GPIA"],"itemData":{"id":1118,"type":"article","title":"Technical/Regulatory Guidance: Remediation Technologies for Perchlorate Contamination in Water and Soil","URL":"http://www.eosremediation.com/download/Perchlorate/ITRC%20PERC-2.pdf","author":[{"literal":"The Interstate Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer

effectively removes the target contaminant, i.e., the contaminant "breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cxQjBTo8","properties":{"formattedCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","plainCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio,

TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed (i.e., operated on a 'throw-away' basis). This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"I0SaZZiL","properties":{"formattedCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],

"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Ion exchange can increase the corrosivity of treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dcLyBjzj","properties":{"formattedCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","plainCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":1079,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":10

79,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1078,"uris":["http://zotero.org/groups/945096/items/BNWD5VQP"],"uri":["http://zotero.org/groups/945096/items/BNWD5VQP"],"itemData":{"id":1078,"type":"article-journal","title":"Rotation ion-exchange system removes perchlorate","page":"454A-455A","volume":"32","journalAbbreviation":"Environ. Sci. Technol.","author":[{"family":"Betts","given":"K.S."}],"issued":{"date-parts":[["1998"]]}}},{"id":1208,"uris":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"uri":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"itemData":{"id":1208,"type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for

management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench-scale tests and full-scale treatment plant studies [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CnYkqct9","properties":{"formattedCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1019,"uris":["http://zotero.org/groups/945096/items/E5WRR4HD"],"uri":["http://zotero.org/groups/945096/items/E5WRR4HD"],"itemData":{"id":1019,"type":"article-journal","title":"Evaluation of electron donors for biological perchlorate removal highlights the importance of diverse perchlorate-reducing populations","container-title":"Environmental Science: Water Research & Technology","page":"1049-1063","volume":"2","author":[{"family":"Kotlarz","given":"N."},{"family":"Upadhyaya","given":"G."},{"family":"Togna","given":"P."},{"family":"Raskin","given":"L."}],"issued":{"date-parts":[["2016"]]}}},{"id":1106,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1106,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online

Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR, respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 µg/L ClO4–. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 µg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-parts":[["2015",12,1]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-

parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}},{"id":1093,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1093,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"

],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nKwIqjde","properties":{"formattedCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA

Annual Conference and

Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."

},"issued":{"date-

parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"

],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"arti

cle-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water

production","container-title":"Journal AWWA","page":"30-

40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litch

field","given":"M.H."}],"issued":{"date-

parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ISPg08cl","properties":{"formattedCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","plainCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","noteIndex":0},"citationItems":[{"id":1047,"uris":["http://zotero.org/groups/945096/items/X3WWHCXS"],"uri":["http://zotero.org/groups/945096/items/X3WWHCXS"],"itemData":{"id":1047,"type":"speech","title":"The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","event-

place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1046,"uris":["http://zotero.org/groups/945096/items/IIXUW45F"],"uri":["http://zotero.org/groups/945096/items/IIXUW45F"],"itemData":{"id":1046,"type":"article","title":"Supporting data for presentation: The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1045,"uris":["http://zotero.org/groups/945096/items/FLVLSXCS"],"uri":["http://zotero.org/groups/945096/items/FLVLSXCS"],"itemData":{"id":1045,"type":"speech","title":"The Impact of Temperature on Anaerobic Biological Perchlorate Treatment","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dugan","given":"N.R."},{"family":"Williams","given":"D.J."},{"family":"Meyer","given":"M."},{"family":"Schneider","given":"R.R."},{"family":"Speth","given":"T.F."},{"family":"Metz","given":"D.H."}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in

bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NDoHjLOr","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTX

Y"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"f4qlOob5","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","noteIndex":0},"citationItems":[{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report

","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ySKwU3Em","properties":{"formattedCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1051,"uris":["http://zotero.org/groups/945096/items/Z7PC3BME"],"uri":["http://zotero.org/groups/945096/items/Z7PC3BME"],"itemData":{"id":1051,"type":"speech","title":"Full-Scale Biological Denitrification Plants in Germany, Austria and Poland","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle,

WA","author":[{"family":"Dordelmann","given":"O."}],"issued":{"date-parts":[["2009",11]]}}},{"id":1026,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1026,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"

],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"edXX3GgQ","properties":{"formattedCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","plainCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":985,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-parts":[["1998"]]}}},{"id":986,"uris":["http://zotero.org/groups/945096/items/YHEV76YW"],"uri":["http://zotero.org/groups/945096/items/YHEV76YW"],"itemData":{"id":986,"type":"paper-conference","title":"Perchlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher-place":"Phoenix,

AZ","event":"American Water Works Association Membrane Technology Conference","event-place":"Phoenix, AZ","author":[{"family":"Nam","given":"S."},{"family":"Kim","given":"S."},{"family":"Choi","given":"H."},{"family":"Yoon","given":""},{"family":"Silverstein","given":"J."},{"family":"Amy","given":"G."}],"issued":{"date-parts":[["2005"]]}}},{"id":992,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":992,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":991,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water. Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in [REF _Ref529958951 \h]. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"J9AlL73G","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance

Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table X-[SEQ Table * ARABIC \s 1]: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, the EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

The SSCT listed in [REF _Ref529958951 \h] include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LHgBHn5b","properties":{"formattedCitation":"(USEPA, 1998)","plainCitation":"(USEPA, 1998)","noteIndex":0},"citationItems":[{"id":1215,"uris":["http://zotero.org/groups/945096/items/399QNBY4"],"uri":["http://zotero.org/groups/945096/items/399QNBY4"],"itemData":{"id":1215,"type":"article","title":"Variance Technology Findings for Contaminants Regulated Before 1996","publisher":"EPA 815–R– 98–003. September","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of

median household income. [REF _Ref529959037 \h] shows the expenditure margins derived for the analysis. These margins show the cap on affordable incremental annual expenditures.

Table X-[SEQ Table * ARABIC \s 1]: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2scXqyv0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"x096Tc8Y","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1225,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1225,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Rg9m81J","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018b)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018b)","noteIndex":0},"citationItems":[{"id":1226,"uris":["http://zotero.org/groups/945096/items/GTI7H6YK"],"uri":["http://zotero.org/groups/945096/items/GTI7H6YK"],"itemData":{"id":1226,"type":"article","title":"CPI--All Urban Consumers (all items), for areas under 50,000 persons","author":[{"family":"Bureau of Labor Statistics (BLS)","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

b. Affordability threshold equals 2.5 percent of MHI.

c. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fS2Ibu6t","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":163,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":163,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[REF _Ref529959069 \h] shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z6GYvRh1","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"18aKvRLD","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":147,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":147,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-

****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-[SEQ Table * ARABIC \s 1]: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8y1WSJT4","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.
a. For perchlorate, the EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA

establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA Sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions

from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant. However, the perchlorate MCL could result in a greater frequency of reporting by certain states. See discussion of Paperwork Reduction Act compliance in Section XVI for more information.

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XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);
- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);
- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);

- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If the EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B below summarizes the method the EPA used to estimate these costs.

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The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section C below summarizes this method used to estimate these benefits.

Section D below provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a), which is available in the docket for the proposed rule. Section XIII summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

Some costs associated with an NPDWR are incurred by all CWS and NTNCWS (e.g. monitoring and reporting) while others are only incurred by systems with perchlorate levels exceeding the MCL. The EPA estimated costs for CWS and NTNCWS to monitor and report perchlorate levels and also estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment because it is the most cost-effective treatment option and easy to operate on a 'throw-away' basis. If site-specific nontreatment options are available and lower cost, then this assumption might overstate costs. The EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring, report results, and apply for waivers. For the purpose of these estimates, the EPA assumed that both small and large systems would require the same amount of time to read the rule, apply for a waiver, and collect a water sample but that it would take large systems twice as long to provide initial training to their staff. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.
1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

Systems will incur monitoring costs over the analysis period. The EPA estimated monitoring frequency based on the proposed initial monitoring requirements, the standard monitoring framework requirements for inorganic contaminants, and the proposed implementation schedule. The estimated number of monitoring samples over the analysis period shown in Table XII-2 reflect the following phases:

1. Initial monitoring; four quarterly samples at every CWS and NTNCWS entry point.

2. Preliminary regular monitoring before waiver application: three regular monitoring samples for every CWS and NTNCWS entry point (collected annually at surface water system entry points and triennially at ground water system entry points).

3. Long-term monitoring at either (a) regular monitoring frequency for entry points at systems not granted waivers (60% of surface water system and 10% of ground water systems), or (b) reduced monitoring frequency for entry points at systems receiving waivers from primacy agencies (40% of surface water systems and 90% of ground water systems), which is one sample during every nine-year compliance monitoring cycle.

Table XII-2: Estimates of Compliance Monitoring Samples by Phase and System Type, Size, and Source Water

Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
1. Initial monitoring (4 quarterly samples in one year)	All CWS and NTNCWS	92,656	370,624
2. Preliminary regular monitoring (3 annual entry point samples for surface water systems and 3 triennial entry point samples for ground water systems)	All CWS and NTNCWS	92,654	277,962
3a. Long-term monitoring, no waiver (annual entry point samples)	60% of large surface water CWS	3,324	86,424
	60% of small surface water CWS and all surface water NTNCWS	6,064	139,472
3a. Long-term monitoring, no waiver (triennial entry point samples)	10% of large ground water CWS	680	4,080
	10% of small ground water CWS and all ground water NTNCWS	7,021	35,105
3b. Long-term monitoring, waiver (1 sample every 9 years)	40% of large surface water CWS	2,216	4,432
	40% of small surface water CWS and all surface water NTNCWS	4,043	8,086
3b. Long-term monitoring, waiver (1 sample every 9 years)	90% of large ground water CWS	6,117	12,234
	90% of small ground water CWS and all ground water NTNCWS	63,189	63,189

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780).
1. The EPA estimated a total of 92,656 entry points based on the total number of potentially affected systems in SDWIS/FED and the average number of entry points per system in the UCMR 1 data by size category and source water. The initial monitoring phase includes all entry points. The EPA assumed that the two entry points with MCL exceedances at the proposed MCL of 56 µg/L would continue to take quarterly samples for the duration of the analysis period, for a total of 232 samples. Thus, they are excluded from the estimates for the subsequent phases of regular and long-term monitoring. Primacy agencies may, however, allow monitoring to return to a regular schedule if treatment process operation can reliably and consistently reduce perchlorate below the MCL.
2. For Phase 3, the estimate of aggregate samples is the product of the number of entry points and the frequency of sampling during the remaining years of the analysis period. For example, large surface water CWS without a waiver conduct long-term annual monitoring for 26 years because they complete preliminary regular monitoring in year 9. In contrast, large ground water CWS without a waiver begin long-term triennial monitoring in year 16 because their preliminary regular monitoring phase lasts for 9 years (3 triennial samples) instead of 3 years (3 annual samples). The estimates also reflect schedule differences by size because large CWS begin monitoring schedules three years earlier than small CWS and all NTNCWS.

To estimate costs to CWSs and NTNCWSs associated with time spent on compliance monitoring and other administrative costs, the EPA generally uses the labor rate[13] for full-time treatment plant operators in CWSs from USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5g8IJ6Eh","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/FHCVSMRC"],"uri":["http://zotero.org/groups/945096/items/FHCVSMRC"],"itemData":{"id":992,"type":"article","title":"Labor Cost for National Drinking Water Rules","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2011"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which vary based on the size of the system.

[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of system entry points that exceed the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[14]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and nontreatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion

[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c) contains more complete discussion of the WBS models and the cost estimating approach.

exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, the EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 μg/L the blending target would be 45 μg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost

curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and Agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-3 summarizes the labor hour assumptions for these activities. The EPA requests comments on these assumptions.

Table XII-3: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)

1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.

2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"C1A8zUkj","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","plainCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"uri":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"itemData":{"id":984,"type":"webpage","title":"Employer Cost for Employee Compensation -- September 2016","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2016"]]}},"label":"book","suffix":"Table 3"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], for a fully loaded hourly wage rate for States of $50.67. The EPA requests comments on these labor rate assumptions.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these

periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mnzEXxZK","properties":{"formattedCitation":"(USEPA, 2008b)","plainCitation":"(USEPA, 2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":998,"uris":["http://zotero.org/groups/945096/items/QSXYHBID"],"uri":["http://zotero.org/groups/945096/items/QSXYHBID"],"itemData":{"id":998,"type":"article","title":"Draft Information Collection Request for the Disinfectants/Disinfection Byproducts, Chemical, and Radionuclides Rule","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2008",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[15]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Q6RKolIZ","properties":{"formattedCitation":"(U.S. Census

[15] For systems with monitoring costs only, household-level costs will be negligible.

Bureau, 2017b)","plainCitation":"(U.S. Census Bureau, 2017b)","noteIndex":0},"citationItems":[{"id":1000,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":1000,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA divided the total annual system-level costs by the number of households served by the system.

C. Method for Estimating Benefits

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-

quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rCNbGglo","properties":{"formattedCitation":"(U.S. Census Bureau, 2017a)","plainCitation":"(U.S. Census Bureau, 2017a)","noteIndex":0},"citationItems":[{"id":189,"uris":["http://zotero.org/groups/945096/items/ZM7S6H44"],"uri":["http://zotero.org/groups/945096/items/ZM7S6H44"],"itemData":{"id":189,"type":"article","title":"Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016.","URL":"https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html#ds","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7XfZyKhY","properties":{"formattedCitation":"(Martin, Hamilton, & Osterman, 2017)","plainCitation":"(Martin, Hamilton, & Osterman, 2017)","noteIndex":0},"citationItems":[{"id":186,"uris":["http://zotero.org/groups/945096/items/MY6LPDKD"],"uri":["http://zotero.org/groups/945096/items/MY6LPDKD"],"itemData":{"id":186,"type":"article","title":"Births in the United States, 2016. NCHS Data Brief No. 287","URL":"https://www.cdc.gov/nchs/data/databriefs/db287.pdf","author":[{"family":"Martin","given":"J.A."},{"family":"Hamilton","given":"B.E."},{"family":"Osterman","given":"M.J.K"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 μg/L and alternative MCLs of 18 μg/L and 90 μg/L. The first step relates changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake. For the BBDR simulations, the

EPA used the 90th percentile ingestion rate to be consistent with the MCLG modeling approach, which may overstate the exposure in the simulation.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"iqyVRL6z","properties":{"formattedCitation":"(Korevaar et al., 2016)","plainCitation":"(Korevaar et al., 2016)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence

quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or

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positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ

decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-4 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

Table XII-4: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2019a).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants that target the thyroid, such as

nitrate, as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XIII provides additional discussion of uncertainties in this analysis.

D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 µg/L, Table XII-5 summarizes the total estimated cost of the proposed rule to water systems and primacy agencies, and Table XII-6 summarizes the estimated per-household cost for the system incurring treatment costs[16]. Table XII-7 summarizes the estimated benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

Table XII-5: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

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{"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-6: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table XII-7: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

For the alternative MCL of 18 µg/L, Table XII-8 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-9 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-10 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

Table XII-8: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

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Detail may not sum to total because of independent rounding.
1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.
2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-9: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

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1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

Table XII-10: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EN9pibZj","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-11 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-12 summarizes the per-

household cost for systems requiring treatment, which vary across the systems. Table XII-13 summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

Table XII-11: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-12: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 µg/L because treatment costs to meet an MCL of 90 µg/L are lower than the costs to meet an MCL of 56 µg/L.

Table XII-13: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Table XII-14 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between an MCL of 56 µg/L and an MCL of 18 µg/L and between an MCL of 90 µg/L and 56 µg/L.

Section 1412(b)(4)(C) of the SDWA requires that when proposing a national primary drinking water regulation, "the Administrator shall publish a determination as to whether the benefits of the maximum contaminant level justify, or do not justify, the costs." The infrequent

occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 µg/L using the best available science and data, the EPA Administrator has determined based upon the available information that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs.

Under these circumstances, Section 1412(b)(6)(A) of the SDWA provides, with exceptions not relevant here, that "the Administrator *may*, after notice and opportunity for public comment promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits." The EPA has evaluated the benefits and costs of alternative MCL values of 18 µg/L and 90 µg/L. However, based upon the available information the Administrator also finds that the benefits of an NPDWR at the alternative MCL values would not justify the resulting rule costs. The alternative MCLs would not increase net benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar. Consistent with the discretion afforded the Agency by SDWA Section 1412(b)(6)(A) to decide whether or not to adjust an MCL to a level where the benefits justify the costs, the EPA is however proposing, and may finalize, the MCL of 56 µg/L notwithstanding the Agency's determination that benefits would not justify the costs.

Table XII-14: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55

56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E0mmmXDK","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA has presented an extensive discussion of the uncertainties in the key analyses informing this proposal in the uncertainty section of the MCLG Approaches Report and the uncertainties section of the Economic Analysis document (*USEPA, 2018b; USEPA, 2019a)*. A summarized description of these uncertainties are presented below.

A. Uncertainty in the MCLG Derivation

Each input into the analysis to inform the MCLG is a decision point associated with uncertainty. There is uncertainty in different aspects of the BBDR model, ranging from structural

and functional relationships to specific parameter values for early pregnancy. There are very few data available to calibrate the pharmacokinetic aspects of the model, particularly at the life stage of interest. Also, the BBDR model does not explicitly consider the effect of the presence of other goitrogens (e.g. thiocyanate, nitrate) or effects of thyroid disease states. Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. Additional uncertainty is introduced by linking the BBDR model estimates of maternal fT4 to altered neurodevelopment in offspring. None of the studies used to evaluate potential adverse neurodevelopmental outcomes in offspring born to hypothyroxinemic mothers was performed in the U.S. None of the studies measured perchlorate exposure. Not all the studies measured iodide levels in the study populations. The state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. There are numerous indices used to assess neurodevelopmental impacts and there is some uncertainty regarding the selection of IQ as the critical endpoint for setting the MCLG.

A recently published paper evaluating the EPA's BBDR model and MCLG Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al., 2019).

B. Uncertainty in the Economic Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2019a). Table XIII-1 provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect[1]
Baseline Occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water).	± (benefits and costs will change in the same direction)
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 µg/L or 90 µg/L and that one small system would exceed 18 µg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than the MCLs that are not captured in the national extrapolation results.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum.	± (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4.	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The EPA used a 90th percentile water intake rate to derive the MCLG and the dose-response equations for the benefits analysis. This approach results in a protective MCLG value, but may overstate intake for the benefits analysis[2].	+ (benefits only)

Description	Potential effect[1]
The IQ valuation uses estimates that the EPA derived using the same approach as Salkever (1995). Results from other IQ valuation studies might result in higher or lower benefit estimates.	± (benefits only)
The benefits analysis is based on a single health endpoint and the value of the endpoint is based solely on lost earnings.	− (benefits only)
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)
The EPA assumed that all entry points requiring treatment would implement ion exchange, which may overestimate costs if non-treatment is an option for one or more entry points or underestimate costs if site-specific conditions result in higher costs at one or more entry points.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	− (costs only)
The EPA assumed that 90% of ground water systems and 40% of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.
2. The EPA did not include a perchlorate dietary dose in the benefits analysis, which would be unchanged between baseline and proposed MCL scenarios if many areas do not irrigate with drinking water. For people who obtain a significant portion of their fruit, vegetables, and milk from areas irrigated with the water from the same sources as the drinking water, we would expect their exposure may drop with the reduction of perchlorate in food products used locally. Because of this and the natural log form of the IQ response function, this approach may slightly understate the avoided IQ decrement estimates.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al., 1991; Pop et al., 1999; Pop et al., 2003; Kooistra et al., 2006)" (p. 10, SAB for the U.S. EPA, 2013). The EPA's literature review identified potential relationships between maternal thyroid hormone alterations and the risk of schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include risks associated with effects of thyroid disorders in adults, including cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints are not monetized in this benefits analysis. The assumptions used to account for the previously mentioned variability of the BBDR model inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above may result in an overestimate of the monetized benefits. Because IQ is a surrogate for broad range of potential neurodevelopmental risks, it is unclear whether the analysis as a whole over- or under-estimates the monetized benefits of a reduction of perchlorate in drinking water.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues will be especially helpful to the EPA in developing a final rule. The EPA specifically requests comment on the following topics.

- The adequacy and uncertainties of the BBDR model developed by the EPA to predict thyroid hormone level changes caused by perchlorate exposure to pregnant women with low iodide intake, including the model and model parameters and assumptions (Section III and Approaches Report).
- The adequacy and uncertainties of the EPA's review and application of the epidemiologic literature to quantify the relationship between thyroid hormone changes in pregnant women and neurodevelopmental effects including the assumptions, the selection of the approach used, and the study used (Section III and Approaches Report).
- The adequacy and uncertainties of the methodology to derive the MCLG including points of departure, assumptions, uncertainty factor, and relative source contribution (Section III and Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water).
- The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.

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- The feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.
- The adequacy of the underlying assumptions and analysis of occurrence (Section VI).
- The costs and availability of Treatment Technologies (Section X).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate costs and describe unquantified costs including the estimates of monitoring frequency, likelihood of systems receiving a monitoring waiver, the administrative labor rate and the operator labor rate. (Section XII and the Health Risk Reduction Cost Analysis).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate benefits and describe unquantified benefits (Section XII and the Health Risk Reduction Cost Analysis).
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's finding in accordance with Section 1412(b)(4)(C) of the SDWA that the benefits of the proposed 56 µg/L MCL for perchlorate do not justify the costs, and the information that supports that determination as described in Section XII of this notice.
- The Administrator's proposal to, consistent with the discretion afforded him by SDWA Section 1412(b)(6)(A), adopt an MCL of 56 µg/L notwithstanding the Agency's SDWA Section 1412(b)(4)(C) determination that the benefits of the MCL would not justify its costs.

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- The Agency's conclusion that no alternative MCL, including the alternative MCL values of 18 µg/L and 90 µg/L discussed above, would "maximize health risk reduction benefits at a cost that is justified by the benefits" and the information and analytical approaches used to arrive at that conclusion. The EPA is especially interested in comments suggesting other approaches to deriving an MCL for which the benefits justify the costs.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on several factors. First, the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern[17] and suggest that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate, but the available data indicates that very few would find it at levels of public health concern. Specifically, perchlorate occurrence information suggests that at an MCL of 56 µg/L only 2 systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Even at an MCL of 18 µg/L, there would only be 15 systems (0.03% of all water systems in the

[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or 90 µg/L, which are the possible levels expected to cause adverse human health effects.

U.S.) that would exceed the regulatory threshold. Only one system would exceed the alternative MCL of 90 µg/L.

The EPA notes that in 2008, the EPA stated in its preliminary regulatory determination that perchlorate did not occur with a frequency and at levels of public health concern in public water systems based upon the health effects and occurrence information available at that time, which indicated that 0.8% of public water system had perchlorate at levels exceeding the HRL of 15 µg/L. The EPA also stated that there was not a meaningful opportunity for a NPDWR to reduce health risks based upon the estimates at that time that 0.9 million people had perchlorate levels above the HRL.

The EPA further notes that the Agency has previously determined CCL1 and CCL2 contaminants did not occur with frequency at levels of public health concern when the percentage of water systems exceeding the HRL were greater than the frequency of perchlorate occurrence level at the proposed MCL (0.004% of all water systems in the U.S.). For example, in 2003 the EPA determined that aldrin did not occur with a frequency and at levels of public health concern based upon data that showed 0.2% of water systems had aldrin at levels greater than the HRL. The EPA also concluded that there was not a meaningful opportunity for health risk reduction for persons served through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 1 million people (USEPA, 2003). In 2008 the EPA determined that DCPA Mono- and Di-Acid degradates did not occur with a frequency and at levels of public health concern based on data that showed 0.03%

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of water systems exceeded the HRL. The EPA also included that there was not a meaningful opportunity for health risk reduction through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 100,000 people (USEPA, 2008e).

SDWA Section 1412(b)(1)(A)(iii) states that the determination regarding the meaningful opportunity is "in the sole judgement of the Administrator" and therefore there may be other factors that contribute to this determination for any given contaminant.

If, after consideration of public comment, the EPA withdraws the perchlorate regulatory determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using its SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authorities, as appropriate. The EPA also requests comments on what guidance it could provide the public if the regulatory determination for perchlorate is withdrawn.

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XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a)* is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in the EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The monitoring information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule

promulgation, the major information requirements concern primacy agency activities to implement the rule including adopting the NPDWR into state regulations, providing training to state and PWS employees, updating their monitoring data systems, and reviewing system monitoring data and waiver requests. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) would not begin until after Year 3 due to the proposed effective date of this rule.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

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An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to the EPA at the public docket established for this rule, which includes the ICR, Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In

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accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 7 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a). Table XII-1 and Table XII-2 show the annual compliance costs of the proposed rule on the small entities by system size for public and private systems, respectively. Based on a comparison of annual costs with annual revenue estimates, the EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2019a).

Table XII-1: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Public CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$224,248	$88 (0.04%)	$94 (0.04%)
Population served 101-500	$197,315	$88 (0.04%)	$94 (0.05%)

Population served 501-3,300	$202,382	$88 (0.04%)	$94 (0.05%)
Population served 3,301-10,000	$1,092,187	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,16]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Revenues include all sources of revenue including water revenue, non-water revenue, and municipal transfers to water systems.

b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

Table XII-2: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Private CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$139,911	$88 (0.06%)	$94 (0.07%)
Population served 101-500	$351,974	$88 (0.03%)	$94 (0.03%)
Population served 501-3,300	$254,706	$88 (0.03%)	$94 (0.03%)
Population served 3,301-10,000	$951,692	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,16]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Revenues include all sources of revenue including water revenue and non-water revenue.
b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of

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Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a webinar with interested tribes on February 28, 2012, to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012a). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women

exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2019a) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply

energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. The EPA methods 314.0, 314.1, 314.2, 331.0,

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and 332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

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XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC, 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (USEPA, 2012; NRC, 2005). On May 29, 2013, the EPA received significant input from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (USEPA, 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking

process for perchlorate (USEPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (USEPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (USEPA 2013a). Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). The EPA provided information to HHS officials on the draft proposed perchlorate regulation and considered HHS input as part of the interagency review described in section XVII.A.

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List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew R. Wheeler,

Administrator.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

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k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."
8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."
9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b),

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141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*******	*******	*******	*******

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Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM])
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.00002
*******	*******	*******	*******

*****

*****

(c)***

(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023, and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must

collect four consecutive quarterly samples at all sampling points between January 1, 2026, and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023, and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution system may use the monitoring data from the compliance monitoring period that began between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be

based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	Methodology[13]	EPA	ASTM[3]	SM[4] (18th, 19th ed.)	SM[4] (20th ed.)	SM Online[22]	Other
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	314.1					
	Two-Dimensional Ion Chromatography with Suppressed	314.2					

	Conductivity Detection Liquid Chromatography Electrospray Ionization Mass Spectrometry Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	 331.0 332.0					
******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

*****

[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the

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Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

Contaminant	Preservative[1]	Container[2]	Time[3]

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*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L
*******	*******

*****

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

*****

(b)***

Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000 persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	**Traditional MCL in mg/L**	**To convert for CCR, multiply by**	**MCL in CCR units**	**MCLG**	**Major sources in drinking water**	**Health effects language**
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						
********	********	********	*******	*******	*******	*******

Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation
*******				
B. Inorganic Chemicals (IOCs)				

*******				
14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			
C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

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[2] MCL – Maximum contaminant level

PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

The EPA Administrator signed the following proposed rule on 5/23/2019, and EPA is submitting it for publication in the Federal Register (FR). While we have taken steps to ensure the accuracy of this Internet version of the proposed rule, it is not the official version of the proposed rule for purposes of public comment. Please refer to the official version in a forthcoming FR publication, which will appear on the Government Printing Office's FDsys website (https://www.gpo.gov/fdsys/). It will also appear on Regulations.gov (https://www.regulations.gov/) in Docket No. EPA-HQ-OW-2019-0780.

Once the official version of this document is published in the FR, this version will be removed from the Internet and replaced with a link to the official version

6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about

perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, the EPA is requesting comment on three alternatives: 1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18 µg/L), 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 µg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011, determination to regulate perchlorate in drinking water based on new information that indicates that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and there may not be a meaningful opportunity for health risk reduction through a drinking water regulation. Under this last alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

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ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at http://www.regulations.gov. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit http://www2.epa.gov/dockets/commenting-epa-dockets.

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This proposed rule is organized as follows:

I. General Information

A. What is the EPA Proposing?

B. Does This Action Apply to Me?

II. Background

A. What is Perchlorate?

B. Statutory Authority

C. Statutory Framework and Regulatory History

III. Assessment and Modeling of the Health Effects of Perchlorate

A. 2008 Preliminary Regulatory Determinations

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

C. Science Advisory Board Recommendations

D. Perchlorate Model Development and Peer Reviews

E. Sensitive Population for Deriving MCLG

F. BBDR Model Specification for the Sensitive Population

G. Epidemiological Literature

H. Identifying a Point of Departure for Developing the MCLG

I. Translate PODs to RfDs

J. Translate RfD into an MCLG

IV. Maximum Contaminant Level Goal and Alternatives

V. Maximum Contaminant Level and Alternatives

VI. Occurrence

VII. Analytical Methods

VIII. Monitoring and Compliance Requirements

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A. What are the Monitoring Requirements?

B. Can States Grant Monitoring Waivers?

C. How are System MCL Violations Determined?

D. When Must Systems Complete Initial Monitoring?

E. Can Systems Use Grandfathered Data to Satisfy the Initial Monitoring Requirement?

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

B. What are the Public Notification Requirements?

X. Treatment Technologies

A. What are the Best Available Technologies?

B. What are the Small System Compliance Technologies?

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

B. What are the State Record Keeping Requirements?

C. What are the State Reporting Requirements?

XII. Health Risk Reduction Cost Analysis

A. Identifying Affected Entities

B. Method for Estimating Costs

C. Method for Estimating Benefits

D. Comparison of Costs and Benefits

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XIII. Uncertainty Analysis

A. Uncertainties in the MCLG Derivation

B. Uncertainties in the Economic Analysis

XIV. Request for Comment on Proposed Rule

XV. Request for Comment on Potential Regulatory Determination Withdrawal

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

C. Paperwork Reduction Act

D. Regulatory Flexibility Act (RFA)

E. Unfunded Mandates Reform Act

F. Executive Order 13132: Federalism

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use

J. National Technology Transfer and Advancement Act of 1995

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of 56 µg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 µg/L.

The EPA is proposing an NPDWR for perchlorate in accordance with its February 11, 2011, (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such

contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is soliciting comment on two alternative MCLG/MCL values of 18 µg/L and 90 µg/L respectively. Third, in light of new considerations that have come to the EPA's attention since it issued its positive regulatory determination in 2011, including information on lower levels of occurrence of perchlorate than the EPA had previously believed to exist and new analysis of the concentration that represents a level of health concern, this action also discusses and requests comment on an alternative action under which the EPA would withdraw its 2011 determination to regulate perchlorate. Under this alternative, there would be no MCLG or NPDWR for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems
State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If

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you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Statutory Framework and Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water system. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems (CWS) and non-

transient, non-community water systems (NTNCWS). The UCMR collects data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556) which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999, 2000b).

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule knows as the sodium/iodide symporter (NIS), which may lead to decreases in two hormones, thyroxine (T3) and triiodothyronine (T4) and increases in thyroid-stimulating hormone (TSH) (National Research Council (NRC), 2005b). Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the recommended National Research Council RfD of 0.7 µg/kg/day for perchlorate. The reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study (Greer, Goodman,

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

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Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability (USEPA, 2005b).

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 µg/L based on the RfD of 0.7 µg/kg/day in making this conclusion (USEPA, 2008a). Based primarily on the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In January 2009 the EPA published an interim health advisory for perchlorate of 15 µg/L, consistent with the HRL derivation for perchlorate of 15 µg/L described above. Health Advisories are non-enforceable and non-regulatory and provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health Advisories provide the public, including the most sensitive populations, with a margin of protection from a lifetime

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of exposure. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (74 FR 41883; USEPA, 2009a). After careful consideration of public comments on the October 2008 and August 2009 notices, on February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011a). The Agency stated then that when considering the alternative HRL benchmarks described in the 2009 notice, the likelihood of perchlorate to occur at levels of concern had significantly increased in comparison to the levels described on the 2008 preliminary negative determination. The EPA concluded that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally described in the 2008 notice.

In its 2011 determination, the Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data for systems in California and Massachusetts using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than October 31, 2018, and finalize an NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water was later extended to May 28, 2019. The consent decree is available in the docket for today's proposed rule.

III. Assessment and Modeling of the Health Effects of Perchlorate

Perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the NIS (ATSDR, 2008; Greer et al., 2002; NRC, 2005; SAB 2013; Taylor et al., 2013). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can

adversely affect thyroid hormone production (SAB for the U.S. EPA, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB for the U.S. EPA, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

The mode of action of perchlorate toxicity has been proposed as follows: exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland through the NIS (NRC, 2005; SAB for the U.S. EPA, 2013). A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that T3 and T4 require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased TSH, the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production (Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016). For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels

during pregnancy, including in the hypothyroxinemic range[2], have been linked to decrements in neurocognitive function in offspring (Alexander et al., 2017; Thompson et al., 2018; Wang et al., 2016). There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate's mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in sensitive populations. Therefore, based on the known mode of action of perchlorate the Agency estimated potential health risks using a novel approach suggested by the EPA's Science Advisory Board (SAB for the U.S. EPA, 2013). The EPA's approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

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[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of T3 and T4, and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency). Based on these findings, the NRC recommended a reference dose of 0.7 μg/kg/day.

Based on NRC's analysis, the EPA established a perchlorate reference dose (RfD) of 0.7 μg/kg/day in 2005 (USEPA, 2005). This value was based on a no observed effect level (NOEL) of 7 μg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

As discussed above, in 2008, the EPA derived an HRL of 15 μg/L using the RfD of 0.7 μg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (i.e., food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse

health effects to the subpopulation identified by the NAS as likely the most sensitive to the effects of perchlorate exposure, fetuses.

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the EPA developed alternative HRLs for other sensitive populations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 µg/L to 47 µg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK)

analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically free T4 (fT4)) that are associated with

maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Reviews

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, i.e., breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). In addition to estimating effects on breast fed infants, several reviewers recommended that the EPA shift the primary focus of its analysis to modeling the exposure implications to the fetus during early pregnancy. This was based on the knowledge that fetuses lack a functioning thyroid gland until approximately 16 gestational weeks and the substantial epidemiological evidence linking early pregnancy low fT4 levels with adverse neurodevelopmental outcomes (Endendijk et al., 2017, Korevaar et al., 2016; Morreale de Escobar, Obregón, & Escobar del Rey, 2004, Pop et al., 1999; Pop et al., 2003). Specifically, the SAB recommended that the EPA use specific sensitive

populations to develop the MCLG for perchlorate: "the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" (SAB for the U.S. EPA, 2013, p. 19).

The EPA considered all recommendations from the 2017 peer review. The previously developed BBDR model describing perchlorate's effects in the third trimester (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b) was calibrated only for that phase of pregnancy, not for the first trimester, and lacked a description of TSH signaling (feedback) that becomes significant as individuals become hypothyroxinemic or hypothyroid. In particular, this signaling was considered necessary to accurately predict responses of women with very low iodine intake, which was also part of the 2017 peer review recommendations. Therefore, the Lumen et al., (2009b) model needed to be revised to address these recommendations and the EPA implemented those changes needed to increase the scientific rigor of the model and modeling results. These modifications include:

- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in January 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches in the draft *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (MCLG Approaches Report) to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018). The 2018 peer review identified a variety of strengths and limitations of the modeling (to be discussed in more detail later in this notice). The peer review panel was largely supportive of the efforts described in the MCLG Approaches Report, as evidenced by the following from the peer review final report:

> *Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).*

The EPA also presented an alternative, population-based approach evaluating the shift in the proportion of the population that would fall below a hypothyroxinemic cut point, given exposure to perchlorate (Section 7 of the MCLG Approaches Report). This

approach does not directly connect the BBDR output to a neurodevelopmental endpoint. However, for pregnant women in early pregnancy, this shift could be related to avoiding an increase in the population of offspring's risk of adverse neurodevelopmental impacts. The 2018 peer review identified strengths associated with this approach, including

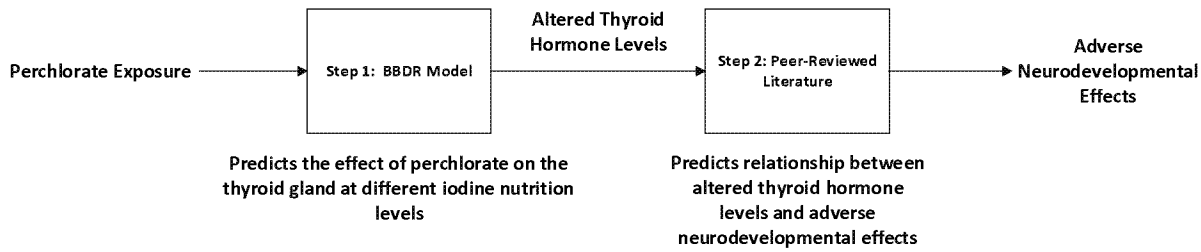
> *1) the central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; 2) this approach encompasses a variety of adverse neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and 3) this approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an adverse neurodevelopmental effect.* (*External Peer Reviewers for U.S. EPA, 2018, p. 7)*

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for an MCLG based on this approach to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The peer-review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. The EPA is requesting public comment in Section XIV on the adequacies and uncertainties of the methodology to derive the MCLG including the decision not to pursue this population-based approach for setting the MCLG.

Based on the comments of the peer reviewers, the EPA's final analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking water (see Figure 1). In summary, because of the known mode of action, the lack of epidemiological studies particularly in the sensitive populations and the direction of the SAB to use a "data-driven approach [which] represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages" (p. 2, SAB 2013 for U.S. EPA), the EPA uses a combination of the BBDR model that simulates perchlorate potential impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail, highlighting each step in which decisions and assumptions were made.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring



Note: Process figure does not imply the strength of scientific evidence.

E. Sensitive Population for Deriving MCLG

SDWA 1412(b)(4)(A) requires MCLGs to be set at a concentration in water "at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." SDWA 1412(b)(3)(C)(V) further requires that the EPA "consider the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." The EPA has interpreted these requirements to establish MCLGs that avoid adverse effects within the portions of the population that are at greater risk of adverse effects from exposure to the contaminant. The EPA is proposing an MCLG that is developed to protect the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of an fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less

effective than for the median individual). The choice of this population is consistent with discussion by the NRC (2005), and the SAB (2013). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" (USEPA, 2017; p. 73). As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 µg/day). Assuming 2 or 4 µg/kg/day of perchlorate, the first trimester hypothyroxinemic

[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 µg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than 75 µg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there are reports in the scientific literature suggesting that minor perturbations in thyroid hormone levels in the first trimester mother may adversely impact her offspring's neurodevelopment. Specifically, some studies show that children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) have a higher risk of reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Man, Brown, & Serunian, 1991; Pop et al., 2003; Pop et al., 1999). Notably these effects are correlated with both degree (Henrichs et al., 2010; Pop et al., 1999) and duration (Pop et al., 2003) of maternal hypothyroxinemia (SAB for the U.S. EPA, 2013, p. 10).

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. This finding is consistent with conclusions by the California Environmental Protection Agency (CalEPA) in

their assessment of a public health goal for perchlorate (California Environmental Protection Agency, 2011, p. 90).

Specifically, two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. Costeira et al., (2011) found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, Henrichs et al., (2010) found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB for the U.S. EPA, 2013). Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in

infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive lifestage and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and
- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal

concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to many other PBPK models. Because perchlorate does not undergo metabolism in vivo (Clewell et al., 2007), potential uncertainty from this factor of the model is avoided since it does not need to be described.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model estimates serum thyroid hormone levels in the mother at specific gestational weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, to be health protective the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG, thereby protecting both this target sensitive population with an adequate margin of safety and those who are less sensitive with an even larger margin of safety.

The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al., (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited (Blount et al., 2006, Steinmaus et al., 2007; Leung, Pearce, & Braverman, 2010). The EPA selected an iodine intake level of 75 µg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 µg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH ranges between 4.51 and 5.41 milli-international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a

[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism (Alexander et al., 2017). Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" (Alexander et al., 2017, p. 332). ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. (2008) is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones (Blount et al., 2006; Steinmaus et al., 2013, 2016). The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in Table III-1.

Table III-1. Summary of BBDR Model Results for fT4 Levels: Pregnant Women at Gestational Week 13, Assuming Low (75 µg/day) Iodine Intake and with Muted TSH feedback strength[a]

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43	5.96	6.56	8.71

	(-2.45%)	(-2.24%)	(-2.04%)	(-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)
5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] pTSH = 0.398; see USEPA, (2018b) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67. All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestation week and did not account for variation in perchlorate and iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (e.g. Blount et al., 2007) and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3). The EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4 for the identified sensitive population, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4 concentrations for women with low fT4 of childbearing age would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et

al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. To protect the most sensitive population from adverse effects, the EPA chose to use the 10th percentile from this distribution of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population[5].

G. Epidemiological Literature

The SAB recommended that the EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Roman et al., 2013; van Mil et al., 2012). These individual studies showing that maternal hypothyroxinemia is associated with offspring neurodevelopment are also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

when considering the entire body of evidence on this topic (Fan & Wu, 2016; Thompson et al., 2018; Wang et al., 2016). Additionally, the American Thyroid Association concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

The EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes given: 1) the body of scientific literature regarding this association, and 2) the SAB recommendation that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25). Instead, the EPA conducted a "methodologic approach to reviewing the literature" to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. More specifically, the EPA only used studies that had sufficient data to show a quantitative relationship between maternal fT4 and a neurodevelopmental outcome. The EPA acknowledges that by not giving any weight to the studies that did not show a quantitative relationship between fT4 and neurodevelopmental outcomes, the Agency may be overestimating the dose of perchlorate that may be associated with adverse neurodevelopmental outcomes. This is a health protective decision that adds to the margin of safety.

Ultimately, the EPA developed a dose-response function that estimates incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

The specifics of this "methodologic approach to reviewing the literature" follow. First, the EPA identified and screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- compatible with the sensitive life stages identified by the NRC and SAB;
- continuous measure of thyroid hormone values (versus categorical values);
- low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- access to underlying data.

Second, using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40

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[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs

studies). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia. Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior and other outcomes. The EPA notes that by selecting the papers that potentially had dose response data the Agency is deviating from the systematic weight of evidence review approach to identify those studies that the SAB recommended we examine to derive the MCLG.

Third, from these 15 papers five were selected for dose response assessment - four related to cognition (Finken et al., 2013; Korevaar et al., 2016; Pop et al., 2003, 1999) and one related to

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for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

behavior (Endendijk, Wijnen, Pop, & van Baar, 2017). The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-response assessment (e.g., dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al., (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

As laid out for the peer reviewers, for each study that met the criteria identified above for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018b). These relationships were either presented in the original published paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from

each study to assure consideration of the populations likely to be at greater risk from the dose of perchlorate associated with a given change in fT4.

Table III-2 provides a summary of the changes in fT4 predicted to produce a 1, 2, and 3 percent decrease in any given neurodevelopmental effect and corresponding perchlorate doses. The choice of 1, 2, and 3% is based on the analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI). Specifically, a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points) equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively (Endendijk et al., 2017; Finken et al., 2013).

These results provide the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (derived from the epidemiologic literature[7]).

[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the MCLG Approaches Report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

Table III-2. Estimated Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopment for the Population of Low-Iodine Intake Women of Reproductive Age Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al., (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1
Korevaar et al., (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8
Pop et al., (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al., (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al., (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al., (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al., (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

H. Identifying a Point of Departure for Developing the MCLG

From the seven analyses presented in Table III-2 above, the EPA chose to use its independent analysis of the Korevaar et al., (2016) data (comprising of 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. There are three reasons for this selection: 1) there is sufficient quantitative data to derive a health impact function for the sensitive population of interest; 2) the analysis adjusts for an appropriate set of confounders, and 3) the neurodevelopmental endpoint – intelligence quotient (IQ) – is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below). The other studies presented in Table III-2 do not provide one or more of these features (USEPA, 2018b).

The five identified papers evaluated a variety of endpoints with Korevaar et al., (2016) evaluating IQ, Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) using the Bayley Scale to evaluate PDI and MDI, Finken, van Eijsden, Loomans, Vrijkotte, and Rotteveel (2013) evaluating the SD of reaction time, and Endendijk, Wijnen, Pop, and van Baar (2017) evaluating anxiety/depression scores using the Child Behavioral Check List (CBCL). The SD of reaction time from Finken et al., (2013) was not well-received by the peer reviewers (External Peer Review for U.S. EPA, 2018) because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al., (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al., (2017) nor the Finken et al., (2013) analyses had functions for the sensitive life stage (i.e., their analyses were based on the full range of fT4 levels and did not concentrate on the impacts of low-end fT4 levels). For these reasons, the Endendijk et al., (2017) and Finken et al., (2013) papers were not selected for further evaluation.

The Korevaar et al., (2016) original and independent analyses are preferable compared to the Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) studies because neither function derived from the Pop et al., studies was adjusted for confounders. Additionally, both

Pop et al., papers have an N < 50 compared to the Korevaar et al., analyses, which have an N of greater than 3,600.[8]

Although the original Korevaar et al., (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al., (2016) EPA reanalysis was chosen over the original analysis because it included modifications to the analysis at the suggestion of the peer review panel. The revised analysis controls for a more parsimonious set of confounders (e.g., previously included variables such as infant gender, maternal parity, birthweight, mother's body mass index (BMI), and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al., (2016) model because of the feedback received during the peer review of the MCLG Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

> *Korevaar et al., [2016] controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of*

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[8] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609 due to the exclusion of subjects with imputed values for maternal fT4.

the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al., (2016) data, and making decisions about data quality and influential data points in the analysis. That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values. Subsequently, the EPA selected the Korevaar et al., (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ [9].

As indicated above, the EPA has utilized a health protective approach to this analysis consistent with the SDWA definition of the MCLG. The peer reviewers commented that this approach was fit-for-purpose. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and

[9] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the MCLG Approaches Report.

neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. As explained earlier, the results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior, and other outcomes such as autism. Among these studies, only 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous

variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al., (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al., (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek et al., 2017; Roman et al., 2013;

Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al., (2011) and Gyllenberg et al., (2016). Although Endendijk et al., (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al., (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al., (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al., (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking.

Not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses (Fan & Wu, 2016; Thompson et al., 2018 and Wang et al., 2016), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears

strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. Therefore, the EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data. In an attempt to minimize uncertainty, the EPA reanalyzed the data collected by Korevaar et al., (2016) using a spline function that estimates a coefficient specifically for the low range of the fT4 data.

There are a variety of neurodevelopmental endpoints used to examine behavior and cognition in children (e.g., intelligence quotient (IQ), motor skills, vocabulary and language development, stimulus responsiveness, etc.). The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al., (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. As such, in the derivation of the MCLG, IQ is a surrogate for a suite of potential neurodevelopmental effects that might occur to the offspring of hypothyroxinemic and iodine deficient mothers.

There are several different tests that are widely used to measure IQ in children, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific

tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

Associations have been found between IQ scores and both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al., (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). Research suggests that children's rearing environment, including parental education, while growing up may increase IQ scores in adolescence by several points (e.g., Kendler et al., 2015).

IQ scores have been used to help diagnose disorders such as intellectual disability and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) IQ scores are used in an individual's comprehensive assessment to determine intellectual disability,

which pairs standardized testing of intelligence with a clinical assessment of adaptive functioning. Intellectual disability is considered for individuals with an IQ score of about 70 or below (American Psychiatric Association, 2013).

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 percent extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint. Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, USEPA, 2012).

For the specific context of setting an MCLG for perchlorate, the EPA made a policy decision to evaluate the level of perchlorate in water associated with a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points). The EPA selected IQ as a surrogate for neurodevelopmental effects based upon its evaluation of the epidemiologic literature describe above. The need to utilize the best available peer reviewed data to inform scientific assumptions and policy choices to meet the statutory

requirements associated with developing an MCLG under the SDWA highlights the challenges associated with regulating chemicals for which potential effects are indirect, and scientific data do not address all uncertainties. The Agency must make a policy decision informed by science, consistent with statutory requirements even in situations where the data do not provide clear choices. To develop the proposed MCLG for perchlorate, the EPA made a policy decision to use a 2 IQ point decrement in the population-distribution of IQ for the sensitive population. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants for which there is concern about potential thyroid effects, either under the SDWA or other statutory frameworks.

Applying these response rates to the results from the reanalysis of Korevaar et al., (2016), results in a POD dose of 3.1 μg/kg/day for a 1 point decrease in the sensitive population's IQ, a POD dose of 6.7 μg/kg/day for a 2 point decrease in the sensitive population's IQ, and a POD dose of 10.8 μg/kg/day for a 3 point decrease in the sensitive population's IQ. These PODs associated with a 1, 2, or 3 point decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the POD is designed to provide an adequate margin of safety for the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 μg/day and a TSH feedback loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the methodological reasons described previously, the EPA believes that the selection of these

parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive population and allows for an adequate margin of safety.

I. Translate PODs to RfDs

When deriving an RfD the EPA evaluates whether to apply uncertainty/variability factors to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002). As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a no-observed-adverse-effect-level (NOAEL), and an incomplete database. The factors are intended to account for: 1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); 2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); 3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); 4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and 5) uncertainty associated with extrapolation when the database is incomplete. (U.S. EPA, 2011b) The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., uncertainty factor (UF) for within-human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. The

approach taken to derive the RfD attempts to address variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.

Further, as discussed in section III.C. of this notice the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However,

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[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the MCLG Approaches Report.

there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. In addition, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is potentially because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et al., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the fetal thyroid begins secreting thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels available to the fetus. Given that the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. Therefore, as described above, the EPA selected an intraspecies UF of 3 to account for the uncertainties in modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant

mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children.

The EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. As noted above, the Agency has opted to apply a UF of 3 to the POD, which adds an adequate margin of safety to the MCLG derivation. Section 4.4.5.3 (p 4-42) of *A Review of the RfD & RfC Processes* recommends reducing the intraspecies UF from a default of 10 "only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)" (p. xviii, USEPA, 2002).The EPA selected a UF of 3 instead of the full 10 because the modeled groups within the population that are identified as likely to be at greater risk to perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother) and has selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake).

Below we list the other uncertainty factors added and the justification.

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.

- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.
- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.
- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).
- The product of all the uncertainty factors (UF_H) is 3 (3 x 1 x 1 x 1 x 1).

Below we generate RfD's for each of the points of departure.

Using the POD of 6.7 µg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.2\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 µg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.0\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

J. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\ \left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 μg/kg/day for a 1 percent decrease in IQ, 2.23 μg/kg/day for a 2 percent decrease in IQ, or 3.6 μg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_W = relative source contribution of drinking water to overall perchlorate exposure.

To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate specific to women of childbearing age (i.e., non-pregnant, non-lactating, 15–44 years of age (0.032 L/kg/day). This decision is consistent with the analysis used in deriving an RSC, which was performed using food consumption information for a population of women of childbearing age from NHANES. The 90th percentile is chosen to account for variability in drinking water ingestion rates, but also adds another layer of health protection for 90% of women (Table III-3).

The EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable. The use of the drinking water intake for 15-44 year old women is consistent with the analysis used in deriving an RSC_W (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the

EPA's Exposure Factors Handbook (USEPA, 2011c) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis.

Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2019c). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in about 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (μg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The details of these assumptions are explained on page 5-5 of the Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (USEPA 2019c). Specifically, the EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the 20 samples included in the TDS data. In order to estimate the 95th percentile from the 20 samples, the EPA used the second-

highest test result for each food to represent the 95th percentile concentration. While simple, this method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine (Carriquiry et al., 2016). The aforementioned method for identifying the 95th percentile concentration of perchlorate from food was selected over other, more "statistically based" methods for estimating percentiles as it avoids the need to assume a distributional shape for the samples. The EPA determined that it was more reliable to assume the empirically derived distribution as the basis for selecting the 95th percentile (i.e., assuming the distribution was equal to the distribution of samples collected in the TDS), as opposed to forcing a distributional shape, such as normal or log-normal, onto the data that may not necessarily be appropriate. With the chosen method, we can at least be sure that the distributional shape is appropriate for the data at hand, whereas by choosing the alternative that assumes a distributional shape, in many instances we would not even be certain of that. The EPA used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 µg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate

consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile perchlorate food concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

The EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III-5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using the EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.0	56%	0.032	18
2.2	80%	0.032	56
3.6	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss, 2-point IQ loss, or a 3-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the NPDWR. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an

MCLG of 56 µg/L based on the rationale and methodology described in Section III above. The derivation of the proposed MCLG uses a point of departure based upon a two percent decrease in IQ for offspring of hypothyroxinemic women of child bearing age have with low iodine intake. The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the subpopulation of interest.

As described in Section III, the EPA has selected model parameters and other factors for the derivation of the MCLG that are health protective, including the focus on the most sensitive life stage. The EPA believes that the selection of the combination of protective parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive subpopulation and allows for an adequate margin of safety. The EPA also acknowledges the uncertainties in the derivation of the proposed (and alternative) MCLGs. The EPA acknowledges in particular the challenge associated with selecting the decrement of IQ that represents an adverse effect at the population level and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement given the absence of robust human epidemiological data directly linking perchlorate exposure to IQ decrements. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

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V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2019b). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018c). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

Because the EPA is taking comment on alternative MCLG values of 18 µg/L and 90 µg/L the Agency evaluated the feasibility of setting an MCL at these levels. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this level under field conditions (USEPA 2018a, 2019b). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative

MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA Section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA

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relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The UCMR 1 is the primary source of occurrence data the EPA relied on to estimate the number of water systems (and associated population) expected to be exposed at levels of perchlorate which could potentially exceed the proposed and alternative MCL levels. Since UCMR 1 data was first used to inform the Agency actions on the 2008 preliminary regulatory determination and the 2011 final regulatory determination, the Agency has modified its analysis of the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions at some States that have enacted perchlorate regulations since the UCMR 1 data was collected. Despite these updates, the EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants (USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to the EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 µg/L for perchlorate in the UCMR.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

In September of 2012, the EPA received a "Request for Correction" letter from the United States Chamber of Commerce regarding information and data (i.e., the occurrence of perchlorate in drinking water) used by the EPA in its 2011 determination to regulate perchlorate. The U.S. Chamber of Commerce letter stated that the EPA relied upon: 1) data that did not comply with data quality guidelines and 2) data that was not representative of current conditions.

In response[12] to the U.S. Chamber of Commerce, the EPA conducted a detailed assessment of the source water sample detections and determined that it was most appropriate to exclude the source water sample detections from the UCMR 1 perchlorate data set when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 perchlorate data set. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 perchlorate data set. As a result of the assessment, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the entry point to the distribution system. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections from 149 PWSs.

Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

In response to the U.S. Chamber of Commerce request, the EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two states. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 (MassDEP, 2006), and

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[12] See the EPA response letter at https://www.epa.gov/sites/production/files/2017-08/documents/12004-response_0.pdf

California promulgated a drinking water standard of 6 μg/L in 2007 (California Department of Public Health, 2007). Systems in these states are now required to keep perchlorate levels in drinking water below their state limits, which are lower than the proposed MCL and alternative MCLs. Therefore, the UCMR 1 sampling results from systems in these states do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. The notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

To update the occurrence data for systems sampled during UCMR 1 from the States of California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

Out of the 540 detections previously described the EPA updated data for 321 detections (320 from California systems and 1 from a Massachusetts system). The convention used by the

EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported compliance monitoring data, if more than one data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were the EPA could not find updated entry point data, then the original data from UCMR 1 for such entry point was kept.

Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 µg/L	15	525	540
Sample measurements > 18 µg/L	1	16	17
Sample measurements > 56 µg/L	0	2	2
Sample measurements > 90 µg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 µg/L	8	328	336
Entry points at which measurements > 18 µg/L	1	16	17
Entry points at which measurements > 56 µg/L	0	2	2
Entry points at which measurements > 90 µg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 µg/L	8	141	149
Systems at which measurements > 18 µg/L	1	14	15
Systems at which measurements > 56 µg/L	0	2	2
Systems at which measurements > 90 µg/L	0	1	1

Source: (USEPA, 2019b). The total row counts and counts of measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population

is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements > 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements > 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements > 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: (USEPA, 2019b). The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or

underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCLs. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: (USEPA, 2019b).

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: (USEPA, 2019b).
1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: (USEPA, 2019b).

In summary, the perchlorate occurrence information suggests that at an MCL of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. One of these two systems would exceed the alternative MCL of 90 µg/L. In addition, at an MCL of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is ''feasible'', the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, the

SDWA directs the EPA to determine that it is economically and technologically feasible to ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain ''criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels.'' (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report (USEPA, 2019b).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of

sample analysis and data reporting. All of the proposed EPA analytical methods provide performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

The EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework set out in 40 CFR 141 Subpart C (Standardized Monitoring Framework). Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. The EPA is proposing that consistent with the standardized monitoring framework water systems would be initially required to monitor quarterly for perchlorate. The EPA is also proposing that based upon the monitoring results States would be able to reduce the monitoring frequency to annually, once every three years or once every nine years if the State concludes that the system is reliably and consistently below the MCL. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point in the next quarter after the violation occurred (40 CFR 141.23(c)(7)). The state may allow the system to return to the reduced monitoring frequency when the state determines that the system is reliably and consistently below the MCL. However, the state cannot make a determination that

the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples below the MCL have been collected (40 CFR 141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the state (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under this proposal, water systems may apply to the state, and states may grant, a 9-year monitoring waiver for perchlorate if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A state may grant a waiver for surface water systems after three rounds of annual monitoring with results less than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

Under this proposal, violations of the perchlorate MCL would be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the perchlorate MCL would be determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than 10,000 persons must collect 4 quarterly samples for perchlorate during the second compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the Standardized Monitoring Framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the third compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the Standardized Monitoring Framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered perchlorate data collected after January 1, 2020, to satisfy the initial monitoring requirements. To satisfy initial perchlorate monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for CWSs serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for NTNCWs and for CWSs serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

A community water system must prepare and deliver to its customers an annual Consumer Confidence Report (CCR) in accordance with requirements in 40 CFR 141 Subpart O.

A CCR provides customers with information about their local drinking water quality as well as information regarding the water system compliance with drinking water regulations. Under this proposal CWSs would be required to report perchlorate information in their CCR.

B. What are the Public Notification Requirements?

All public water systems must give the public notice for all violations of NPDWRs and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, per 40 CFR 141.202(b)(1), notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation under this proposal.

X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by states to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other

means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in states issuing small system variances under Section 1412(e) of the SDWA.

The Agency solicits public comment on the choice of available treatment technologies discussed in this section.

A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new

well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water (Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008). The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, i.e., the contaminant "breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base

polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes (Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010).

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed (i.e., operated on a 'throw-away' basis). This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste (Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010). Ion exchange can increase the corrosivity of treated water (Berlien, 2003; Betts, 1998; USEPA, 2005b) because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for

bench-scale tests and full-scale treatment plant studies (Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017). Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 (T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017). Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible (Dugan, 2010b, 2010a; Dugan et al., 2009). This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus (Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009).

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is

non-toxic and can be discharged to a sanitary sewer (U.S. Department of Defense (U.S. DoD), 2008, 2009) or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides (Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017). The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across

multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent (Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005). While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water. Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in Table X-1. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability (USEPA, 2018a).

Table X-1: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, the EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

The SSCT listed in Table X-1 include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules (USEPA, 1998). The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the

difference between baseline household water costs and a threshold equal to 2.5% of median household income. Table X-2 shows the expenditure margins derived for the analysis. These margins show the cap on affordable incremental annual expenditures.

Table X-2: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a)
a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates (U.S. Census Bureau, 2010) stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons (Bureau of Labor Statistics (BLS), 2018b).
b. Affordability threshold equals 2.5 percent of MHI.
c. Household water costs derived from 2006 Community Water System Survey (USEPA, 2009c), based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

Table X-3 shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a) and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c). Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-3: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a), which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.
a. For perchlorate, the EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA Sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance

of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant. However, the perchlorate MCL could result in a greater frequency of reporting by certain states. See discussion of Paperwork Reduction Act compliance in Section XVI for more information.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance

with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);

- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);
- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If the EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B below summarizes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section C below summarizes this method used to estimate these benefits.

Section D below provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a), which is available in the docket for the proposed rule. Section XIII summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

Some costs associated with an NPDWR are incurred by all CWS and NTNCWS (e.g. monitoring and reporting) while others are only incurred by systems with perchlorate levels exceeding the MCL. The EPA estimated costs for CWS and NTNCWS to monitor and report

perchlorate levels and also estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment because it is the most cost-effective treatment option and easy to operate on a 'throw-away' basis. If site-specific nontreatment options are available and lower cost, then this assumption might overstate costs. The EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring, report results, and apply for waivers. For the purpose of these estimates, the EPA assumed that both small and large systems would require the same amount of time to read the rule, apply for a waiver, and collect a water sample but that it would take large systems twice as long to provide initial training to their staff. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.

1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

Systems will incur monitoring costs over the analysis period. The EPA estimated monitoring frequency based on the proposed initial monitoring requirements, the standard monitoring framework requirements for inorganic contaminants, and the proposed implementation schedule. The estimated number of monitoring samples over the analysis period shown in Table XII-2 reflect the following phases:

1. Initial monitoring; four quarterly samples at every CWS and NTNCWS entry point.

2. Preliminary regular monitoring before waiver application: three regular monitoring samples for every CWS and NTNCWS entry point (collected annually at surface water system entry points and triennially at ground water system entry points).

3. Long-term monitoring at either (a) regular monitoring frequency for entry points at systems not granted waivers (60% of surface water system and 10% of ground water systems), or (b) reduced monitoring frequency for entry points at systems receiving waivers from primacy agencies (40% of surface water systems and 90% of ground water systems), which is one sample during every nine-year compliance monitoring cycle.

Table XII-2: Estimates of Compliance Monitoring Samples by Phase and System Type, Size, and Source Water

Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
1. Initial monitoring (4 quarterly samples in one year)	All CWS and NTNCWS	92,656	370,624

Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
2. Preliminary regular monitoring (3 annual entry point samples for surface water systems and 3 triennial entry point samples for ground water systems)	All CWS and NTNCWS	92,654	277,962
3a. Long-term monitoring, no waiver (annual entry point samples)	60% of large surface water CWS	3,324	86,424
	60% of small surface water CWS and all surface water NTNCWS	6,064	139,472
3a. Long-term monitoring, no waiver (triennial entry point samples)	10% of large ground water CWS	680	4,080
	10% of small ground water CWS and all ground water NTNCWS	7,021	35,105
3b. Long-term monitoring, waiver (1 sample every 9 years)	40% of large surface water CWS	2,216	4,432
	40% of small surface water CWS and all surface water NTNCWS	4,043	8,086
3b. Long-term monitoring, waiver (1 sample every 9 years)	90% of large ground water CWS	6,117	12,234
	90% of small ground water CWS and all ground water NTNCWS	63,189	63,189

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780).

1. The EPA estimated a total of 92,656 entry points based on the total number of potentially affected systems in SDWIS/FED and the average number of entry points per system in the UCMR 1 data by size category and source water. The initial monitoring phase includes all entry points. The EPA assumed that the two entry points with MCL exceedances at the proposed MCL of 56 µg/L would continue to take quarterly samples for the duration of the analysis period, for a total of 232 samples. Thus, they are excluded from the estimates for the subsequent phases of regular and long-term monitoring. Primacy agencies may, however, allow monitoring to return to a regular schedule if treatment process operation can reliably and consistently reduce perchlorate below the MCL.

2. For Phase 3, the estimate of aggregate samples is the product of the number of entry points and the frequency of sampling during the remaining years of the analysis period. For example, large surface water CWS without a waiver conduct long-term annual monitoring for 26 years because they complete preliminary regular monitoring in year 9. In contrast, large ground water CWS without a waiver begin long-term triennial monitoring in year 16 because their preliminary regular monitoring phase lasts for 9 years (3 triennial samples) instead of 3 years (3 annual samples). The estimates also reflect schedule differences by size because large CWS begin monitoring schedules three years earlier than small CWS and all NTNCWS.

To estimate costs to CWSs and NTNCWSs associated with time spent on compliance monitoring and other administrative costs, the EPA generally uses the labor rate[13] for full-time treatment plant operators in CWSs from USEPA (2011c), which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of system entry points that exceed the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[14]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and

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[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c) contains more complete discussion of the WBS models and the cost estimating approach.

nontreatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, the EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships

between these values (USEPA, 2000b). The Agency assumed blending of treated water and untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 μg/L the blending target would be 45 μg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and Agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-3 summarizes the labor hour assumptions for these activities. The EPA requests comments on these assumptions.

Table XII-3: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)
1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.
2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report (Bureau of Labor Statistics (BLS), 2016 Table 3), for a fully loaded hourly wage rate for States of $50.67. The EPA requests comments on these labor rate assumptions.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these

periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with USEPA (2008b), the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and

annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[15]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size (U.S. Census Bureau, 2017b). The EPA divided the total annual system-level costs by the number of households served by the system.

C. Method for Estimating Benefits

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes,

[15] For systems with monitoring costs only, household-level costs will be negligible.

including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent (U.S. Census Bureau, 2017a). The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) (Martin, Hamilton, & Osterman, 2017).

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 μg/L and alternative MCLs of 18 μg/L and 90 μg/L. The first step relates changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of

pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake. For the BBDR simulations, the EPA used the 90th percentile ingestion rate to be consistent with the MCLG modeling approach, which may overstate the exposure in the simulation.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the Korevaar et al., (2016) study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-4 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

Table XII-4: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2019a).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants that target the thyroid, such as nitrate, as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion exchange, biological treatment, and reverse

osmosis) can also remove co-occurring nitrate from drinking water. Section XIII provides additional discussion of uncertainties in this analysis.

D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 µg/L, Table XII-5 summarizes the total estimated cost of the proposed rule to water systems and primacy agencies, and Table XII-6 summarizes the estimated per-household cost for the system incurring treatment costs[16]. Table XII-7 summarizes the estimated benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

Table XII-5: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-6: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80

Source: (USEPA, 2019a).

Table XII-7: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: (USEPA, 2019a)

For the alternative MCL of 18 µg/L, Table XII-8 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-9 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-10 summarizes the quantified benefits. At this threshold, one entry point for one small system in the

UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

Table XII-8: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.
2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-9: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

Source: (USEPA, 2019a)
1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

Table XII-10: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: (USEPA, 2019a)

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-11 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-12 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-13 summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

Table XII-11: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-12: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

Source: (USEPA, 2019a). There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 µg/L because treatment costs to meet an MCL of 90 µg/L are lower than the costs to meet an MCL of 56 µg/L.

Table XII-13: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

Source: (USEPA, 2019a)

Table XII-14 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total

costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between an MCL of 56 µg/L and an MCL of 18 µg/L and between an MCL of 90 µg/L and 56 µg/L.

Section 1412(b)(4)(C) of the SDWA requires that when proposing a national primary drinking water regulation, "the Administrator shall publish a determination as to whether the benefits of the maximum contaminant level justify, or do not justify, the costs." The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 µg/L using the best available science and data, the EPA Administrator has determined based upon the available information that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs.

Under these circumstances, Section 1412(b)(6)(A) of the SDWA provides, with exceptions not relevant here, that "the Administrator *may*, after notice and opportunity for public comment promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits." The EPA has evaluated the benefits and costs of alternative MCL values of 18 µg/L and 90 µg/L. However, based upon the available information the Administrator also finds that the benefits of an NPDWR at the alternative MCL values would not justify the resulting rule costs. The alternative MCLs would not increase net benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar. Consistent with the discretion afforded

the Agency by SDWA Section 1412(b)(6)(A) to decide whether or not to adjust an MCL to a level where the benefits justify the costs, the EPA is however proposing, and may finalize, the MCL of 56 µg/L notwithstanding the Agency's determination that benefits would not justify the costs.

Table XII-14: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA has presented an extensive discussion of the uncertainties in the key analyses informing this proposal in the uncertainty section of the MCLG Approaches Report and the uncertainties

section of the Economic Analysis document (*USEPA, 2018b; USEPA, 2019a)*. A summarized description of these uncertainties are presented below.

A. Uncertainty in the MCLG Derivation

Each input into the analysis to inform the MCLG is a decision point associated with uncertainty. There is uncertainty in different aspects of the BBDR model, ranging from structural and functional relationships to specific parameter values for early pregnancy. There are very few data available to calibrate the pharmacokinetic aspects of the model, particularly at the life stage of interest. Also, the BBDR model does not explicitly consider the effect of the presence of other goitrogens (e.g. thiocyanate, nitrate) or effects of thyroid disease states. Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. Additional uncertainty is introduced by linking the BBDR model estimates of maternal fT4 to altered neurodevelopment in offspring. None of the studies used to evaluate potential adverse neurodevelopmental outcomes in offspring born to hypothyroxinemic mothers was performed in the U.S. None of the studies measured perchlorate exposure. Not all the studies measured iodide levels in the study populations. The state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. There are numerous indices used to assess neurodevelopmental impacts and there is some uncertainty regarding the selection of IQ as the critical endpoint for setting the MCLG.

A recently published paper evaluating the EPA's BBDR model and MCLG Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al., 2019).

B. Uncertainty in the Economic Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2019a). Table XIII-1 provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect[1]
Baseline Occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water).	± (benefits and costs will change in the same direction)
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 µg/L or 90 µg/L and that one small system would exceed 18 µg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than the MCLs that are not captured in the national extrapolation results.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum.	± (benefits only)

Description	Potential effect[1]
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4.	– (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The EPA used a 90th percentile water intake rate to derive the MCLG and the dose-response equations for the benefits analysis. This approach results in a protective MCLG value, but may overstate intake for the benefits analysis[2].	+ (benefits only)
The IQ valuation uses estimates that the EPA derived using the same approach as Salkever (1995). Results from other IQ valuation studies might result in higher or lower benefit estimates.	± (benefits only)
The benefits analysis is based on a single health endpoint and the value of the endpoint is based solely on lost earnings.	– (benefits only)
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)
The EPA assumed that all entry points requiring treatment would implement ion exchange, which may overestimate costs if non-treatment is an option for one or more entry points or underestimate costs if site-specific conditions result in higher costs at one or more entry points.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	– (costs only)
The EPA assumed that 90% of ground water systems and 40% of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.

2. The EPA did not include a perchlorate dietary dose in the benefits analysis, which would be unchanged between baseline and proposed MCL scenarios if many areas do not irrigate with drinking water. For people who obtain a significant portion of their fruit, vegetables, and milk from areas irrigated with the water from the same sources as the drinking water, we would expect their exposure may drop with the reduction of perchlorate in food products used locally. Because of this and the natural log form of the IQ response function, this approach may slightly understate the avoided IQ decrement estimates.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al., 1991; Pop et al., 1999; Pop et al., 2003; Kooistra et al., 2006)" (p. 10, SAB for the U.S. EPA, 2013). The EPA's literature review identified potential relationships between maternal thyroid hormone alterations and the risk of schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include risks associated with effects of thyroid disorders in adults, including cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These

additional potential health endpoints are not monetized in this benefits analysis. The assumptions used to account for the previously mentioned variability of the BBDR model inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above may result in an overestimate of the monetized benefits. Because IQ is a surrogate for broad range of potential neurodevelopmental risks, it is unclear whether the analysis as a whole over- or under-estimates the monetized benefits of a reduction of perchlorate in drinking water.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues will be especially helpful to the EPA in developing a final rule. The EPA specifically requests comment on the following topics.

- The adequacy and uncertainties of the BBDR model developed by the EPA to predict thyroid hormone level changes caused by perchlorate exposure to pregnant women with low iodide intake, including the model and model parameters and assumptions (Section III and Approaches Report).
- The adequacy and uncertainties of the EPA's review and application of the epidemiologic literature to quantify the relationship between thyroid hormone changes in pregnant women and neurodevelopmental effects including the assumptions, the selection of the approach used, and the study used (Section III and Approaches Report).

- The adequacy and uncertainties of the methodology to derive the MCLG including points of departure, assumptions, uncertainty factor, and relative source contribution (Section III and Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water).
- The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.
- The feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.
- The adequacy of the underlying assumptions and analysis of occurrence (Section VI).
- The costs and availability of Treatment Technologies (Section X).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate costs and describe unquantified costs including the estimates of monitoring frequency, likelihood of systems receiving a monitoring waiver, the administrative labor rate and the operator labor rate. (Section XII and the Health Risk Reduction Cost Analysis).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate benefits and describe unquantified benefits (Section XII and the Health Risk Reduction Cost Analysis).
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.

- The Administrator's finding in accordance with Section 1412(b)(4)(C) of the SDWA that the benefits of the proposed 56 µg/L MCL for perchlorate do not justify the costs, and the information that supports that determination as described in Section XII of this notice.
- The Administrator's proposal to, consistent with the discretion afforded him by SDWA Section 1412(b)(6)(A), adopt an MCL of 56 µg/L notwithstanding the Agency's SDWA Section 1412(b)(4)(C) determination that the benefits of the MCL would not justify its costs.
- The Agency's conclusion that no alternative MCL, including the alternative MCL values of 18 µg/L and 90 µg/L discussed above, would "maximize health risk reduction benefits at a cost that is justified by the benefits" and the information and analytical approaches used to arrive at that conclusion. The EPA is especially interested in comments suggesting other approaches to deriving an MCL for which the benefits justify the costs.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on several factors. First, the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern[17] and suggest that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. The

[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or 90 µg/L, which are the possible levels expected to cause adverse human health effects.

proposed regulation would require over sixty thousand public water systems to monitor for perchlorate, but the available data indicates that very few would find it at levels of public health concern. Specifically, perchlorate occurrence information suggests that at an MCL of 56 µg/L only 2 systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Even at an MCL of 18 µg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. Only one system would exceed the alternative MCL of 90 µg/L.

The EPA notes that in 2008, the EPA stated in its preliminary regulatory determination that perchlorate did not occur with a frequency and at levels of public health concern in public water systems based upon the health effects and occurrence information available at that time, which indicated that 0.8% of public water system had perchlorate at levels exceeding the HRL of 15 µg/L. The EPA also stated that there was not a meaningful opportunity for a NPDWR to reduce health risks based upon the estimates at that time that 0.9 million people had perchlorate levels above the HRL.

The EPA further notes that the Agency has previously determined CCL1 and CCL2 contaminants did not occur with frequency at levels of public health concern when the percentage of water systems exceeding the HRL were greater than the frequency of perchlorate occurrence level at the proposed MCL (0.004% of all water systems in the U.S.). For example, in 2003 the EPA determined that aldrin did not occur with a frequency and at levels of public health concern based upon data that showed 0.2% of water systems had aldrin at levels greater than the

HRL. The EPA also concluded that there was not a meaningful opportunity for health risk reduction for persons served through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 1 million people (USEPA, 2003). In 2008 the EPA determined that DCPA Mono- and Di-Acid degradates did not occur with a frequency and at levels of public health concern based on data that showed 0.03% of water systems exceeded the HRL. The EPA also included that there was not a meaningful opportunity for health risk reduction through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 100,000 people (USEPA, 2008e).

SDWA Section 1412(b)(1)(A)(iii) states that the determination regarding the meaningful opportunity is "in the sole judgement of the Administrator" and therefore there may be other factors that contribute to this determination for any given contaminant.

If, after consideration of public comment, the EPA withdraws the perchlorate regulatory determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using its SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authorities, as appropriate. The EPA also requests comments on what guidance it could provide the public if the regulatory determination for perchlorate is withdrawn.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a)* is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in the EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The monitoring information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule

promulgation, the major information requirements concern primacy agency activities to implement the rule including adopting the NPDWR into state regulations, providing training to state and PWS employees, updating their monitoring data systems, and reviewing system monitoring data and waiver requests. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) would not begin until after Year 3 due to the proposed effective date of this rule.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to the EPA at the public docket established for this rule, which includes the ICR, Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In

accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 7 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a). Table XII-1 and Table XII-2 show the annual compliance costs of the proposed rule on the small entities by system size for public and private systems, respectively. Based on a comparison of annual costs with annual revenue estimates, the EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2019a).

Table XII-1: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Public CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$224,248	$88 (0.04%)	$94 (0.04%)
Population served 101-500	$197,315	$88 (0.04%)	$94 (0.05%)

Population served 501-3,300	$202,382	$88 (0.04%)	$94 (0.05%)
Population served 3,301-10,000	$1,092,187	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)
a. Based on the CWSS (USEPA, 2009c Table 65) and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers (BLS, 2018a). Revenues include all sources of revenue including water revenue, non-water revenue, and municipal transfers to water systems.
b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

Table XII-2: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Private CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$139,911	$88 (0.06%)	$94 (0.07%)
Population served 101-500	$351,974	$88 (0.03%)	$94 (0.03%)
Population served 501-3,300	$254,706	$88 (0.03%)	$94 (0.03%)
Population served 3,301-10,000	$951,692	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)
a. Based on the CWSS (USEPA, 2009c Table 65) and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers (BLS, 2018a). Revenues include all sources of revenue including water revenue and non-water revenue.
b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year

costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to

monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a webinar with interested tribes on February 28, 2012, to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012a). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA

evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2019a) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further,

the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. The EPA methods 314.0, 314.1, 314.2, 331.0, and 332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC, 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (USEPA, 2012; NRC, 2005). On May 29, 2013, the EPA received significant input

from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (USEPA, 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking process for perchlorate (USEPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (USEPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (USEPA 2013a). Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). The EPA provided information to HHS officials on the draft proposed

perchlorate regulation and considered HHS input as part of the interagency review described in section XVII.A.

XVIII. References

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ED_005043_00060974-00151

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Webster, T. D., & Crowley, T. J. (2016, June). *Biological treatment of perchlorate in groundwater*. Presented at the AWWA Annual Conference and Exposition.

Webster, T. D., & Litchfield, M. H. (2017). Full-scale biological treatment of nitrate and perchlorate for potable water production. *Journal AWWA*, *109*(5), 30–40.

Wu, X., & Blute, N. K. (2010, March). *Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant*. Presented at the 2010 California-Nevada AWWA Spring Conference, Hollywood, CA.

Yoon, J., Amy, G., & Yoon, Y. (2005). Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes. *Water Science and Technology*, *51*(6–7), 327–334.

Yoon, J., Yoon, Y., Amy, G., & Her, N. (2005). Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions. *Journal of Environmental Engineering*, 726–733.

Zhang, X., Yao, B., Li, C., Mao, J., Wang, W., Xie, X., … Shan, Z. (2016). Reference intervals of thyroid function during pregnancy: self-sequential longitudinal study versus cross-sectional study. *Thyroid*, *26*(12), 1786–1793. https://doi.org/10.1089/thy.2016.0002

[National Primary Drinking Water Regulations: Proposed Perchlorate Rule; Proposed Rule; Page 146 of 163]

List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew R. Wheeler,

Administrator.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."
8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."
9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b),

141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*******	*******	*******	*******

Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM])
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.00002
*******	*******	*******	*******

*****

*****

(c)***

(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023, and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must

collect four consecutive quarterly samples at all sampling points between January 1, 2026, and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023, and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution system may use the monitoring data from the compliance monitoring period that began between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be

based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	Methodology[13]	EPA	ASTM[3]	SM[4] (18th, 19th ed.)	SM[4] (20th ed.)	SM Online[22]	Other
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	314.1					
	Two-Dimensional Ion Chromatography with Suppressed	314.2					

	Conductivity Detection Liquid Chromatography Electrospray Ionization Mass Spectrometry Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	331.0 332.0					
******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

*****

[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the

Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

Contaminant	Preservative[1]	Container[2]	Time[3]

*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L
*******	*******

*****

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

*****

(b)***

Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000 persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	**Traditional MCL in mg/L**	**To convert for CCR, multiply by**	**MCL in CCR units**	**MCLG**	**Major sources in drinking water**	**Health effects language**
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						
********	********	********	*******	*******	*******	*******

Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation
*******				
B. Inorganic Chemicals (IOCs)				

*******				
14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			
C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

[2] MCL – Maximum contaminant level

PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/18/2020 3:23:00 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: RE: 2 perchlorate documents -- for your records
Attachments: Perchlorate Reductions 2-13-20_rk.docx

Hi Eric, please see attached document. It incorporates your suggested edits and addresses your questions.

I am also waiting for some additional feedback form OSWER on the table they provided, as they way it reads now it appears to show several entries for the same mitigation site. Depending on their feedback we might have to update that table.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Tuesday, February 18, 2020 10:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Yes I'll check with Sam and get back to you.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 18, 2020 10:07 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: 2 perchlorate documents -- for your records

Lisa:
I sent the attached comments to Lisa Christ on Thursday but I don't think I received a revised document. Since Lisa is out today, can you check with the Team to get me a revised today?
Thanks
Eric

From: Burneson, Eric
Sent: Thursday, February 13, 2020 2:05 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thank You Lisa
I have a few comments/edits on the perchlorate reduction document in the attached.
Eric

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: 2 perchlorate documents -- for your records

Eric – just wanted to put both documents in one place for you. Both have been reviewed by Jennifer and Christina. Lisa

---

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Tiago, Joseph [Tiago.Joseph@epa.gov]
Sent: 5/23/2019 2:50:26 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Evalenko, Sandy [Evalenko.Sandy@epa.gov]
Subject: RE: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]
Attachments: SignedPerchlorateActionMemo052319.pdf; Perchlorate Action Memo 5-22-19 .docx

Attached is the PDF of the signed Action memo and the clean final version of the memo – Steph please upload this into CMS.

From: Tiago, Joseph
Sent: Thursday, May 23, 2019 10:48 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Subject: RE: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]

On it. Do we have OGC concurrence? Thx!

From: Burneson, Eric
Sent: Thursday, May 23, 2019 10:46 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Subject: FW: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]

Joe can you make the copies and send the package per Stephanie's instructions below using the file that Sam just sent?

From: Flaharty, Stephanie
Sent: Wednesday, May 22, 2019 3:50 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>
Subject: RE: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]

Ok Sam, please use the version that I sent to make any other edits.

Once OMB clears the package we need a single-sided print out (and three double-side copies) for the package. The final FRN then needs to be added to CMS.

Sandy, the revised action memo (Word file) also needs to be added in CMS. When we date the memo, a PDF needs to be placed in CMS.

Thanks to all,
Steph

From: Hernandez-Quinones, Samuel
Sent: Wednesday, May 22, 2019 3:39 PM

To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]
Importance: High

Sandy/Steph,

We are still doing a QA of the document concurrently with OMB review, I have a few additional minor edits that are not captured on the version that Steph transmitted to Sandy at 3:15pm.

I want to ask that you wait until we have input from OMB to decide if any other edit is needed (in addition to the ones I have incorporated into the latest version) before sending forward. I will send you the revised file when we receive clearance.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Flaharty, Stephanie
Sent: Wednesday, May 22, 2019 3:15 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Thompkins, Anita <Thompkins.Anita@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Corr, Elizabeth <Corr.Elizabeth@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Zipf, Lynn <Zipf.Lynn@epa.gov>
Subject: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]
Importance: High

Sandy,

This is to forward the NPDWR for the Proposed Perchlorate Rule package's electronic suite of files. As we discussed, Joe is on his way to Janita with the Action Memo for Dave to sign, so that when we hear from OMB, we can move the package right away. All files are in CMS, including the most current version of the FRN.

Thanks as always for your assistance in moving this forward !

Steph

MEMORANDUM

SUBJECT: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (Tier 1 Action; SAN 5555; RIN 2040-AF28) – **ACTION MEMORANDUM**

FROM: David P. Ross
Assistant Administrator (4101M)

THRU: Office of Policy (1803A)
Office of Executive Secretariat (1105A)

TO: Andrew J. Wheeler
Administrator (1101A)

PURPOSE

Attached for your signature is a proposed rule, titled "National Primary Drinking Water Regulations: Proposed Perchlorate Rule." We recommend signature and publication of this notice to solicit public comment on the EPA's proposal to establish a national primary drinking water regulation (NPDWR) and a non-enforceable maximum contaminant level goal (MCLG) for perchlorate under the Safe Drinking Water Act (SDWA). The proposed NPDWR includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L (56 µg/L), which is proposed to be set at a level equal to the proposed MCLG. The EPA is seeking comment in the attached notice on whether the Agency should consider setting the perchlorate MCLG and MCL at alternative values of 0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). The EPA is also seeking comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water.

DEADINE/TIMELINE

In February 2011, the EPA published a final determination to regulate perchlorate in drinking water. Section 1412(b)(1)(A) of the SDWA requires that the EPA issue a proposed NPDWR within 24 months of the final regulatory determination and a final NPDWR within 18 months after the proposal. However, when the EPA consulted with the Science Advisory Board (SAB), the Agency received recommendations that the EPA prepare a pharmacokinetic model (i.e., a biologically based dose-response model [BBDR]) to predict the effects of perchlorate exposure on the thyroid function in pregnant women and their children, to develop the MCLG for perchlorate. The EPA collaborated with Food and Drug Administration scientists to perform the modeling recommended by the SAB and completed the analysis and associated peer reviews in March 2018.

In February 2016, the Natural Resources Defense Council (NRDC) filed a lawsuit for failure of the EPA to perform its mandatory duties of proposing and finalizing a regulation for perchlorate in accordance with timelines provided in the SDWA. The court-approved consent decree established deadlines for the EPA to sign a proposed rule by October 31, 2018, and a final rule by December 19, 2019.

The EPA was granted an extension on the consent decree for signature of the proposed rule until April 30, 2019. However, due to a partial government shutdown in early 2019, an additional extension was given for signature of the proposed rule until May 28, 2019. The EPA is addressing the consent decree requirements to sign a NPDWR and issue a MCLG for perchlorate in this proposed rule by May 28, 2019.

OVERVIEW

Perchlorate is an inorganic anion which occurs naturally. It is also manufactured as an oxidizer for rockets, missiles, and fireworks and can be an impurity in hypochlorite disinfectants. The public may be exposed to perchlorate through food and drinking water. When exposed, perchlorate interferes with the thyroid gland by inhibiting iodide uptake, which impacts the production of thyroid hormones that are crucial for normal growth and development. Poor iodide uptake in pregnant and lactating women is linked to delayed development and decreased learning capabilities in their infants.

The EPA proposes: (1) to establish a NPDWR and a MCLG and MCL of 0.056 mg/L (56 µg/L) for perchlorate based on avoiding IQ decrements of 2 points or greater in the most sensitive population, the children of pregnant women with low iodide intake, (2) requirements for water systems to conduct monitoring and reporting on perchlorate and to provide information on perchlorate levels to consumers, and (3) requirements for primacy agencies that implement the Public Water System Supervision program under the SDWA. The proposal includes a list of treatment technologies to enable water systems to comply with the MCL, including affordable technologies for small systems.

In the preamble to the proposed rule, the EPA presents the results of its economic analysis and the Agency's conclusion that the benefits of the proposed regulation do not justify the costs. The EPA seeks comment on whether the Agency should set the MCLG and MCL for perchlorate at alternative values of 0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). These alternatives would avoid IQ decrements of 1 or 3 points, respectively, in the most sensitive population and include a margin of safety. Furthermore, the EPA seeks comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water based on the new information that indicate perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Under this alternative, the EPA would not issue a final MCLG or NPDWR for perchlorate.

The EPA has determined that the National Primary Drinking Water Regulations: Proposed Perchlorate Rule does not have disproportionately high and adverse human health or environmental effects on minority populations, low-income populations and/or indigenous peoples, as specified in Executive Order 12898 (59 FR 7629, February 16, 1994), which establishes federal executive policy on environmental justice. This action would increase the

level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

ANTICIPATED PUBLIC STAKEHOLDER RESPONSE

The EPA expects a variety of reactions and responses from stakeholders. Public health and environmental groups may state that proposed regulation is not sufficiently protective and that the EPA does not have the authority to withdraw a determination to regulate a contaminant under the SDWA. These groups may claim that the regulatory process, established in the 1996 SDWA amendments, is not functioning as intended because the EPA has not yet regulated a contaminant identified through the Contaminant Candidate List and Regulatory Determinations processes. Some stakeholders may be critical of the scientific analysis used to inform the derivation of the perchlorate MCLG and the estimate of benefits from the proposed regulation. Industry groups, including the American Water Works Association, the Perchlorate Study Group, the American Chemistry Council, and the U.S. Chamber of Commerce may state that the models have too much uncertainty and variability to be used to establish a drinking water standard.

INTERNAL DEVELOPMENT AND REVIEW PROCESS

The EPA workgroup consists of representatives from the Office of Water, the Office of Children's Health Protection, the Office of General Counsel, the Office of Policy, the Office of Research and Development, the Office of Land and Emergency Management, and the Office of Chemical Safety and Pollution Prevention. The Office of Water sought review and input of the draft *Federal Register* notice from this workgroup prior to submission for interagency review.

INTERAGENCY REVIEW

The Office of Management and Budget (OMB) initiated review of the *Federal Register* notice: "National Primary Drinking Water Regulations: Proposed Perchlorate Rule" on April 15, 2019, and the EPA has addressed any comments made during the review. Edits made during OMB review are in the public docket.

IMPACTS

The EPA estimates this proposed rule would impose an annual cost burden between $9.7 and $10.3 million. Approximately $3.1 to $3.2 million of that annual cost will be borne by states (and the Navajo Tribe) that have primacy to oversee implementation of the requirements. Between $6.6 and $7.1 million of the annual cost will be borne by public water systems and their rate payers. Monitoring and administration requirements amounted to most of the annual cost. The EPA estimates that very few systems will have to install or operate treatment to comply with the regulation.

The EPA determined that the proposed regulation will result in annual costs that are less than one percent of revenue for small public water systems affected by this proposed rule. The average annual costs range from $88 to $94 for these systems. The EPA determined that the compliance costs for this action in any given year are less than the threshold set in the Unfunded Mandates Reform Act ($100 million in expenditures to state, local, and tribal governments in aggregate or to the private sector).

PEER REVIEW
The Office of Water followed the EPA peer review policy with respect to the underlying scientific BBDR model used to derive an MCLG for perchlorate in this regulatory action. As stated above, the EPA sought recommendations from the SAB for developing the proposed MCLG.

To ensure that the EPA had implemented the SAB recommendations, the Agency convened an independent peer review panel to evaluate the BBDR models in 2017. The EPA considered all the recommendations from the 2017 peer review and implemented those needed to increase the scientific rigor of the model and modeling results.

The EPA convened a second, independent peer review panel in 2018 to evaluate the updates to the BBDR model. The EPA also presented several approaches to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects, using evidence from the epidemiological literature. The January 2018 peer review concluded that "the current models are fit for purpose to determine an MCLG."

RECOMMENDATION
I recommend that you sign the attached rulemaking, "National Primary Drinking Water regulations: Proposed Perchlorate Rule."

Attachment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 23 2019

OFFICE OF WATER

MEMORANDUM

SUBJECT: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (Tier 1 Action; SAN 5555; RIN 2040-AF28) – **ACTION MEMORANDUM**

FROM: David P. Ross
Assistant Administrator (4101M)

THRU: Office of Policy (1803A)
Office of Executive Secretariat (1105A)

TO: Andrew J. Wheeler
Administrator (1101A)

PURPOSE

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Internet Address (URL) • http://www.epa.gov
Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Postconsumer, Process Chlorine Free Recycled Paper

In February 2016, the Natural Resources Defense Council (NRDC) filed a lawsuit for failure of the EPA to perform its mandatory duties of proposing and finalizing a regulation for perchlorate in accordance with timelines provided in the SDWA. The court-approved consent decree established deadlines for the EPA to sign a proposed rule by October 31, 2018, and a final rule by December 19, 2019.

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OVERVIEW

Perchlorate is an inorganic anion which occurs naturally. It is also manufactured as an oxidizer for rockets, missiles, and fireworks and can be an impurity in hypochlorite disinfectants. The public may be exposed to perchlorate through food and drinking water. When exposed, perchlorate interferes with the thyroid gland by inhibiting iodide uptake, which impacts the production of thyroid hormones that are crucial for normal growth and development. Poor iodide uptake in pregnant and lactating women is linked to delayed development and decreased learning capabilities in their infants.

The EPA proposes: (1) to establish a NPDWR and a MCLG and MCL of 0.056 mg/L (56 µg/L) for perchlorate based on avoiding IQ decrements of 2 points or greater in the most sensitive population, the children of pregnant women with low iodide intake, (2) requirements for water systems to conduct monitoring and reporting on perchlorate and to provide information on perchlorate levels to consumers, and (3) requirements for primacy agencies that implement the Public Water System Supervision program under the SDWA. The proposal includes a list of treatment technologies to enable water systems to comply with the MCL, including affordable technologies for small systems.

In the preamble to the proposed rule, the EPA presents the results of its economic analysis and the Agency's conclusion that the benefits of the proposed regulation do not justify the costs. The EPA seeks comment on whether the Agency should set the MCLG and MCL for perchlorate at alternative values of 0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). These alternatives would avoid IQ decrements of 1 or 3 points, respectively, in the most sensitive population and include a margin of safety. Furthermore, the EPA seeks comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water based on the new information that indicates perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Under this alternative, the EPA would not issue a final MCLG or NPDWR for perchlorate.

The EPA has determined that the National Primary Drinking Water Regulations: Proposed Perchlorate Rule does not have disproportionately high and adverse human health or environmental effects on minority populations, low-income populations and/or indigenous peoples, as specified in Executive Order 12898 (59 FR 7629, February 16, 1994), which establishes federal executive policy on environmental justice. This action would increase the

level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

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The EPA expects a variety of reactions and responses from stakeholders. Public health and environmental groups may state that proposed regulation is not sufficiently protective and that the EPA does not have the authority to withdraw a determination to regulate a contaminant under the SDWA. These groups may claim that the regulatory process, established in the 1996 SDWA amendments, is not functioning as intended because the EPA has not yet regulated a contaminant identified through the Contaminant Candidate List and Regulatory Determinations processes. Some stakeholders may be critical of the scientific analysis used to inform the derivation of the perchlorate MCLG and the estimate of benefits from the proposed regulation. Industry groups, including the American Water Works Association, the Perchlorate Study Group, the American Chemistry Council, and the U.S. Chamber of Commerce may state that the models have too much uncertainty and variability to be used to establish a drinking water standard.

INTERNAL DEVELOPMENT AND REVIEW PROCESS

The EPA workgroup consists of representatives from the Office of Water, the Office of Children's Health Protection, the Office of General Counsel, the Office of Policy, the Office of Research and Development, the Office of Land and Emergency Management, and the Office of Chemical Safety and Pollution Prevention. The Office of Water sought review and input of the draft *Federal Register* notice from this workgroup prior to submission for interagency review.

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IMPACTS

The EPA estimates this proposed rule would impose an annual cost burden between $9.7 and $10.3 million. Approximately $3.1 to $3.2 million of that annual cost will be borne by states (and the Navajo Tribe) that have primacy to oversee implementation of the requirements. Between $6.6 and $7.1 million of the annual cost will be borne by public water systems and their rate payers. Monitoring and administration requirements amounted to most of the annual cost. The EPA estimates that very few systems will have to install or operate treatment to comply with the regulation.

The EPA determined that the proposed regulation will result in annual costs that are less than one percent of revenue for small public water systems affected by this proposed rule. The average annual costs range from $88 to $94 for these systems. The EPA determined that the compliance costs for this action in any given year are less than the threshold set in the Unfunded Mandates Reform Act ($100 million in expenditures to state, local, and tribal governments in aggregate or to the private sector).

ED_005043_00061044-00003

PEER REVIEW

The Office of Water followed the EPA peer review policy with respect to the underlying scientific BBDR model used to derive an MCLG for perchlorate in this regulatory action. As stated above, the EPA sought recommendations from the SAB for developing the proposed MCLG.

To ensure that the EPA had implemented the SAB recommendations, the Agency convened an independent peer review panel to evaluate the BBDR models in 2017. The EPA considered all the recommendations from the 2017 peer review and implemented those needed to increase the scientific rigor of the model and modeling results.

The EPA convened a second, independent peer review panel in 2018 to evaluate the updates to the BBDR model. The EPA also presented several approaches to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects, using evidence from the epidemiological literature. The January 2018 peer review concluded that "the current models are fit for purpose to determine an MCLG."

RECOMMENDATION

I recommend that you sign the attached rulemaking, "National Primary Drinking Water regulations: Proposed Perchlorate Rule."

Attachment

ED_005043_00061044-00004

Message

From: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Sent: 5/22/2019 7:14:48 PM
To: Evalenko, Sandy [Evalenko.Sandy@epa.gov]
CC: Thompkins, Anita [Thompkins.Anita@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Corr, Elizabeth [Corr.Elizabeth@epa.gov]; Brown, Sineta [Brown.Sineta@epa.gov]; Fields, Wanda [Fields.Wanda@epa.gov]; Zipf, Lynn [Zipf.Lynn@epa.gov]
Subject: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]
Attachments: Perchlorate Proposed Rule Transmittal OD to AA.pdf; Perchlorate Action Memo 5-21-19.docx; Perchlorate Proposed Rule.Action Memo.OD initialed.pdf; Perchlorate Proposed Rule.cover form.pdf; Perchlorate Proposed Rule.FRN typesetting request.funded.pdf; NPDWR for the Proposed Perchlorate Rule.docx

Importance: High

Sandy,

This is to forward the NPDWR for the Proposed Perchlorate Rule package's electronic suite of files. As we discussed, Joe is on his way to Janita with the Action Memo for Dave to sign, so that when we hear from OMB, we can move the package right away. All files are in CMS, including the most current version of the FRN.

Thanks as always for your assistance in moving this forward !

Steph

ENVI RONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, the EPA is requesting comment on three alternatives: 1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18

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μg/L), 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 μg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011 determination to regulate perchlorate in drinking water based on new information that indicates that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and there may not be a meaningful opportunity for health risk reduction through a drinking water regulation. Under this last alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at [HYPERLINK "http://www.regulations.gov"]. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not

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consider comments or comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit [HYPERLINK "http://www2.epa.gov/dockets/commenting-epa-dockets"].

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This proposed rule is organized as follows:

I. General Information

A. What is the EPA Proposing?

B. Does This Action Apply to Me?

II. Background

A. What is Perchlorate?

B. Statutory Authority

C. Statutory Framework and Regulatory History

III. Assessment and Modeling of the Health Effects of Perchlorate

A. 2008 Preliminary Regulatory Determinations

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

C. Science Advisory Board Recommendations

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D. Perchlorate Model Development and Peer Reviews

E. Sensitive Population for Deriving MCLG

F. BBDR Model Specification for the Sensitive Population

G. Epidemiological Literature

H. Identifying a Point of Departure for Developing the MCLG

I. Translate PODs to RfDs

J. Translate RfD into an MCLG

IV. Maximum Contaminant Level Goal and Alternatives

V. Maximum Contaminant Level and Alternatives

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VII. Analytical Methods

VIII. Monitoring and Compliance Requirements

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B. Can States Grant Monitoring Waivers?

C. How are System MCL Violations Determined?

D. When Must Systems Complete Initial Monitoring?

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A. What are the Consumer Confidence Report Requirements?

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X. Treatment Technologies

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A. What are the Best Available Technologies?

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XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

B. What are the State Record Keeping Requirements?

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XII. Health Risk Reduction Cost Analysis

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B. Method for Estimating Costs

C. Method for Estimating Benefits

D. Comparison of Costs and Benefits

XIII. Uncertainty Analysis

A. Uncertainties in the MCLG Derivation

B. Uncertainties in the Economic Analysis

XIV. Request for Comment on Proposed Rule

XV. Request for Comment on Potential Regulatory Determination Withdrawal

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

C. Paperwork Reduction Act

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D. Regulatory Flexibility Act (RFA)

E. Unfunded Mandates Reform Act

F. Executive Order 13132: Federalism

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use

J. National Technology Transfer and Advancement Act of 1995

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate in public water supplies. The EPA

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proposes an MCLG of 56 μg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 μg/L.

The EPA is proposing an NPDWR for perchlorate in accordance with its February 11, 2011 (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is soliciting comment on two alternative MCLG/MCL values of 18 μg/L and 90 μg/L respectively. Third, in light of new considerations that have come to the EPA's attention since it issued its positive regulatory determination in 2011, including information on lower levels of occurrence of perchlorate than the EPA had previously believed to exist and new analysis of the concentration that represents a level of health concern, this action also discusses and requests comment on an alternative action under which the EPA would withdraw its 2011 determination to regulate perchlorate. Under this alternative, there would be no MCLG or NPDWR for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

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Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems
State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water.

B. Statutory Authority

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Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Statutory Framework and Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within

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two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water system. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems (CWS) and non-transient, non-community water systems (NTNCWS). The UCMR collects data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999 the EPA published its first UCMR (64 FR 50556) which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999, 2000b).

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule knows as the sodium/iodide symporter (NIS), which may lead to decreases in two hormones, thyroxine (T3) and triiodothyronine (T4) and increases in thyroid-stimulating hormone (TSH) [ADDIN ZOTERO_ITEM CSL_CITATION

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

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{"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the recommended National Research Council RfD of 0.7 µg/kg/day for perchlorate. The reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in

humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not

present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA, 2008a)","plainCitation":"(USEPA, 2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and

information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Based primarily on the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In January 2009 the EPA published an interim health advisory for perchlorate of 15 µg/L, consistent with the HRL derivation for perchlorate of 15 µg/L described above. Health Advisories are non-enforceable and non-regulatory and provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health Advisories provide the public, including the most sensitive populations, with a margin of protection from a lifetime of exposure. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

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In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (74 FR 41883; USEPA, 2009a). After careful consideration of public comments on the October 2008 and August 2009 notices, on February 11, 2011 the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011a). The Agency stated then that when considering the alternative HRL benchmarks described in the 2009 notice, the likelihood of perchlorate to occur at levels of concern had significantly increased in comparison to the levels described on the 2008 preliminary negative determination. The EPA concluded that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally described in the 2008 notice.

In its 2011 determination, the Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data did not comply with

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data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data for systems in California and Massachusetts using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than October 31, 2018, and finalize an NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water was later extended to May 28, 2019. The consent decree is available in the docket for today's proposed rule.

III. Assessment and Modeling of the Health Effects of Perchlorate

Perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the protein that transports iodide with the NIS from blood to the thyroid gland (ATSDR, 2008; Greer et al., 2002; NRC, 2005; SAB 2013; Taylor et al. 2015). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB for the U.S. EPA, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her

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offspring (SAB for the U.S. EPA, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

More specifically, exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland through the NIS (NRC, 2005; SAB for the U.S. EPA, 2013). A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that T3 and T4 require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased TSH, the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"eF6zWm7L","properties":{"formattedCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","plainCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","noteIndex":0},"citationItems":[{"id":428,"uris":["http://zotero.org/groups/945096/items/UIANA947"],"uri":["http://zotero.org/groups/945096/items/UIANA947"],"itemData":{"id":428,"type":"bill","title":"Toxicological Profile for

Perchlorates","author":[{"family":"ATSDR","given":""}],"issued":{"date-parts":[["2008"]]}}},{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid tormone levels in adolescent and adult men and women living in the United States","container-title":"Environmental Health Perspectives","page":"1865-1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]}}},{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the national health and nutrition examination survey 2007-8","container-title":"Environmental research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate,

thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors

..."","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID: 23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]}}},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy, including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low

environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L. Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-

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9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to decrements in neurocognitive function in offspring (Alexander et al., 2017; Thompson et al., 2018; Wang et al., 2016). There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016;

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[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate's mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in sensitive populations. Therefore, based on the known mode of action of perchlorate the Agency estimated potential health risks using a novel approach suggested by the EPA's Science Advisory Board (SAB for the U.S. EPA, 2013). The EPA's approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of T3 and T4, and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency). Based on these findings, the NRC recommended a reference dose of 0.7 μg/kg/day.

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Based on NRC's analysis, the EPA established a perchlorate reference dose (RfD) of 0.7 μg/kg/day in 2005 (USEPA, 2005). This value was based on a no observed effect level (NOEL) of 7 μg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

As discussed above, in 2008, the EPA derived an HRL of 15 μg/L using the RfD of 0.7 μg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (i.e., food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the subpopulation identified by the NAS as likely the most sensitive to the effects of perchlorate exposure, fetuses.

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the EPA developed alternative HRLs for other sensitive populations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

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The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 μg/L to 47 μg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;

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- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically free T4 (fT4)) that are associated with maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Reviews

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive

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life stages identified by the SAB, i.e., breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). In addition to estimating effects on breast fed infants, several reviewers recommended that the EPA shift the primary focus of its analysis to modeling the exposure implications to the fetus during early pregnancy. This was based on the knowledge that fetuses lack a functioning thyroid gland until approximately 16 gestational weeks and the substantial epidemiological evidence linking early pregnancy low fT4 levels with adverse neurodevelopmental outcomes [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-

U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. Specifically, the SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: "the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" (SAB for the U.S. EPA, 2013, p. 19).

The EPA considered all recommendations from the 2017 peer review. The previously developed BBDR model describing perchlorate's effects in the third trimester (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b) was calibrated only for that phase of pregnancy, not for the first trimester, and lacked a description of TSH signaling (feedback) that becomes significant as individuals become hypothyroxinemic or hypothyroid. In particular, this signaling was considered necessary to accurately predict responses of women with very low iodine intake, which was also part of the 2017 peer review recommendations. Therefore, the Lumen et al. (2009b) model needed to be revised to address these recommendations and the EPA implemented those changes needed to increase the scientific rigor of the model and modeling results. These modifications include:

- extending the model to early pregnancy;

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- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in January 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches in the draft *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (MCLG Approaches Report) to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018). The 2018 peer review identified a variety of strengths and limitations of the modeling (to be discussed in more detail later in this notice). The peer review panel was largely supportive of the efforts described in the MCLG Approaches Report, as evidenced by the following from the peer review final report:

> *Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-*

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reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).

The EPA also presented an alternative, population-based approach evaluating the shift in the proportion of the population that would fall below a hypothyroxinemic cut point, given exposure to perchlorate (Section 7 of the MCLG Approaches Report). This approach does not directly connect the BBDR output to a neurodevelopmental endpoint. However, for pregnant women in early pregnancy, this shift could be related to avoiding an increase in the population of offspring's risk of adverse neurodevelopmental impacts. The 2018 peer review identified strengths associated with this approach, including

> *1) the central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; 2) this approach encompasses a variety of adverse neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and 3) this approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an adverse neurodevelopmental effect. (External Peer Reviewers for U.S. EPA, 2018, p. 7)*

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for an MCLG based on this approach to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The

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peer-review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. The EPA is requesting public comment in Section XIV on the adequacies and uncertainties of the methodology to derive the MCLG including the decision not to pursue this population-based approach for setting the MCLG.

Based on the comments of the peer reviewers, the EPA's final analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking water (see Figure 1). In summary, because of the known mode of action, the lack of epidemiological studies particularly in the sensitive populations and the direction of the SAB to use a "data-driven approach [which] represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages" (p. 2, SAB 2013 for U.S. EPA), the EPA uses a combination of the BBDR model that simulates perchlorate potential impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental

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outcomes in children. The following sections describe the approach in greater detail, highlighting each step in which decisions and assumptions were made.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring

[EMBED Visio.Drawing.15]

Note: Process figure does not imply the strength of scientific evidence.

E. Sensitive Population for Deriving MCLG

SDWA 1412(b)(4)(A) requires MCLGs to be set at a concentration in water "at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." SDWA 1412(b)(3)(C)(V) further requires that the EPA "consider the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." The EPA has interpreted these requirements to establish MCLGs that avoid adverse effects within the portions of the population that are at greater risk of adverse effects from exposure to the contaminant. The EPA is proposing an MCLG that is developed to protect the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 μg/kg/day), low fT4 levels (i.e., 10th percentile of an fT4 distribution for individuals with 75 μg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The choice of this population is consistent with discussion by the NRC (2005), and the SAB (2013). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) will also be

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protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-number>246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

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As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 µg/day). Assuming 2 or 4 µg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 µg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than 75 µg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there are reports in the scientific literature suggesting that minor perturbations in thyroid hormone levels in the first trimester mother may adversely impact her offspring's neurodevelopment. Specifically, some studies show that children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) have a higher risk of reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Notably these effects are correlated with both

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[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

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degree [ADDIN EN.CITE ADDIN EN.CITE.DATA] and duration [ADDIN EN.CITE <EndNote><Cite><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(Pop et al., 2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] of maternal hypothyroxinemia [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>`; p. 10</Suffix><DisplayText>(SAB, 2013; p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-

authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. This finding is consistent with conclusions by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><Prefix>CalEPA`, </Prefix><Suffix>`; p. 90</Suffix><DisplayText>(CalEPA, 2015; p. 90)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency (CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

Specifically, two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. [HYPERLINK \l "_ENREF_9" \o "Costeira, 2011 #7"] found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, [HYPERLINK \l "_ENREF_17" \o "Henrichs, 2010 #928"] found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB for the U.S. EPA, 2013). Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring

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of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive lifestage and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and
- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to many other PBPK models. Because perchlorate does not

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undergo metabolism in vivo (Clewell et al., 2007), potential uncertainty from this factor of the model is avoided since it does not need to be described.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model estimates serum thyroid hormone levels in the mother at specific gestational weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, to be health protective the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG, thereby protecting both this target sensitive population with an adequate margin of safety and those who are less sensitive with an even larger margin of safety.

The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al., (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>1160</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-

number>1160</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206437">1160</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce,</author><author>Braverman</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice and Research: Clinical Endocrinology and Metabolism</secondary-title><alt-title>Best Pract Res Clin Endocrinol Metab</alt-title><short-title>Best Practice and Research: Clinical Endocrinology and Metabolism</short-title></titles><alt-periodical><full-title>Best Pract Res Clin Endocrinol Metab</full-title></alt-periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn>ISSN 1521-690X
EISSN 1532-1908</isbn><label>755955</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1016/j.beem.2009.08.009</url></related-urls></urls><electronic-resource-num>10.1016/j.beem.2009.08.009</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The EPA selected an iodine intake level of 75 μg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 μg/day, which represents approximately the 5th percentile of the NHANES distribution. At

50 µg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH

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[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><Pages>332</Pages><DisplayText>(Alexander et al., 2017, p. 332)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American journal of obstetrics and gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-

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ranges between 4.51 and 5.41 milli-international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones[ADDIN EN.CITE ADDIN EN.CITE.DATA]. The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally

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title></periodical><pages>62-e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

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weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in [REF _Ref517525852 \h * MERGEFORMAT].

Table III-[SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 Levels: Pregnant Women at Gestational Week 13, Assuming Low (75 µg/day) Iodine Intake and with Muted TSH feedback strength[a][]

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)
5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] pTSH = 0.398; see USEPA, (2018b) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67. All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestation week and did not account for variation in perchlorate and iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (e.g. Blount et al. 2007) and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3). The EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

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When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4 for the identified sensitive population, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4 concentrations for women with low fT4 of childbearing age would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. To protect the most sensitive population from adverse effects, the EPA chose to use the 10th percentile from this distribution of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population[5].

G. Epidemiological Literature

The SAB recommended that the EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

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(Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Román et al., 2013; van Mil et al., 2012). These individual studies showing that maternal hypothyroxinemia is associated with offspring neurodevelopment are also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Additionally, the American Thyroid Association concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

The EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes given: 1) the body of scientific literature regarding this association, and 2) the SAB recommendation that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25). Instead, the EPA conducted a "methodologic approach to reviewing the literature" to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in

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neurodevelopmental outcomes. More specifically, the EPA only used studies that had sufficient data to show a quantitative relationship between maternal fT4 and a neurodevelopmental outcome. The EPA acknowledges that by not giving any weight to the studies that did not show a quantitative relationship between fT4 and neurodevelopmental outcomes, the Agency may be overestimating the dose of perchlorate that may be associated with adverse neurodevelopmental outcomes. This is a health protective decision that adds to the margin of safety.

Ultimately, the EPA developed a dose-response function that estimates incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

The specifics of this "methodologic approach to reviewing the literature" follow. First, the EPA identified and screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- compatible with the sensitive life stages identified by the NRC and SAB;
- continuous measure of thyroid hormone values (versus categorical values);
- low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- access to underlying data.

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Second, using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40 studies). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia. Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior and other outcomes. The EPA notes that by selecting the papers that potentially had

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[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

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dose response data the Agency is deviating from the systematic weight of evidence review approach to identify those studies that the SAB recommended we examine to derive the MCLG.

Third, from these 15 papers five were selected for dose response assessment - four related to cognition[ADDIN EN.CITE ADDIN EN.CITE.DATA] and one related to behavior [ADDIN EN.CITE <EndNote><Cite><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(Endendijk, Wijnen, Pop, & van Baar, 2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk, J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar, A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories during pregnancy and child behavioral problems</title><secondary-title>Horm Behav</secondary-title></titles><periodical><full-title>Horm Behav</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-response assessment (e.g., dose-response results were presented as “per standard deviation of fT4” but the standard deviation

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needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al. (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

As laid out for the peer reviewers, for each study that met the criteria identified above for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018b). These relationships were either presented in the original published paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to assure consideration of the populations likely to be at greater risk from the dose of perchlorate associated with a given change in fT4.

Table III-2 provides a summary of the changes in fT4 predicted to produce a 1, 2, and 3 percent decrease in any given neurodevelopmental effect and corresponding perchlorate doses. The choice of 1, 2, and 3% is based on the analyses for IQ, Mental Development Index (MDI),

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and Psychomotor Development Index (PDI). Specifically, a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points) equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively (Endendijk et al., 2017; Finken et al., 2013).

These results provide the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (derived from the epidemiologic literature[7]).

Table III-2. Estimated Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopment for the Population of Low-Iodine Intake Women of Reproductive Age Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al. (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1
Korevaar et al. (2016) EPA	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8

[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the MCLG Approaches Report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

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Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
independent analysis									
Pop et al. (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al. (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al. (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al. (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al. (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

H. Identifying a Point of Departure for Developing the MCLG

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From the seven analyses presented in this table, the EPA chose to use its independent analysis of the Korevaar et al., (2016) data (comprising of 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. There are three reasons for this selection: 1) there is sufficient quantitative data to derive a health impact function for the sensitive population of interest; 2) the analysis adjusts for an appropriate set of confounders, and 3) the neurodevelopmental endpoint – intelligence quotient (IQ) – is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below). The other studies presented in Table III-2 do not provide one or more of these features (USEPA, 2018b).

The five identified papers evaluated a variety of endpoints with Korevaar et al., (2016) evaluating IQ, Pop, Kuijpens, et al. (1999) and Pop, Brouwers, et al. (2003) using the Bayley Scale to evaluate PDI and MDI, Finken, van Eijsden, Loomans, Vrijkotte, and Rotteveel (2013) evaluating the SD of reaction time, and Endendijk, Wijnen, Pop, and van Baar (2017) evaluating anxiety/depression scores using the Child Behavioral Check List (CBCL). The SD of reaction time from Finken et al. (2013) was not well-received by the peer reviewers (External Peer Review for U.S. EPA, 2018) because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al. (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al. (2017) nor the Finken et al. (2013) analyses had functions for the sensitive life stage (i.e., their analyses were based on the full range of fT4 levels and did not concentrate on

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the impacts of low-end fT4 levels). For these reasons, the Endendijk et al. (2017) and Finken et al. (2013) papers were not selected for further evaluation.

The Korevaar et al., (2016) original and independent analyses are preferable compared to the Pop, Kuijpens, et al. (1999) and Pop, Brouwers, et al. (2003) studies because neither function derived from the Pop et al. studies was adjusted for confounders. Additionally, both Pop et al. papers have an N < 50 compared to the Korevaar et al., analyses, which have an N of greater than 3,600.[8]

Although the original Korevaar et al., (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al., (2016) EPA reanalysis was chosen over the original analysis because it included modifications to the analysis at the suggestion of the peer review panel. The revised analysis controls for a more parsimonious set of confounders (e.g., previously included variables such as infant gender, maternal parity, birthweight, mother's body mass index (BMI), and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al., (2016) model because of the feedback received during the peer review of the MCLG Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

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[8] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609 due to the exclusion of subjects with imputed values for maternal fT4.

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Korevaar et al., [2016] controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al., (2016) data, and making decisions about data quality and influential data points in the analysis. That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values. Subsequently, the EPA selected the Korevaar et al., (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ [9].

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[9] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the MCLG Approaches Report.

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As indicated above, the EPA has utilized a health protective approach to this analysis consistent with the SDWA definition of the MCLG. The peer reviewers commented that this approach was fit-for-purpose. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. As explained earlier, the results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior, and other outcomes such as autism. Among these studies, only 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Furthermore, not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature

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review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. Therefore, the EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data. In an attempt to minimize uncertainty, the EPA reanalyzed the data collected by Korevaar et al., (2016) using a spline function that estimates a coefficient specifically for the low range of the fT4 data.

There are a variety of neurodevelopmental endpoints used to examine behavior and cognition in children (e.g., intelligence quotient (IQ), motor skills, vocabulary and language development, stimulus responsiveness, etc.). The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al., (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. As such, in the derivation of the MCLG, IQ is a surrogate for a suite of potential neurodevelopmental effects that might occur to the offspring of hypothyroxinemic and iodine deficient mothers.

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There are several different tests that are widely used to measure IQ in children, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

Associations have been found between IQ scores and both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al. (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). Research suggests that children's rearing environment, including parental education, while growing up may increase IQ scores in adolescence by several points (e.g., Kendler et al. 2015).

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IQ scores have been used to help diagnose disorders such as intellectual disability and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) IQ scores are used in an individual's comprehensive assessment to determine intellectual disability, which pairs standardized testing of intelligence with a clinical assessment of adaptive functioning. Intellectual disability is considered for individuals with an IQ score of about 70 or below (American Psychiatric Association, 2013).

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, the EPA often uses a percentage change value in noncancer risk assessment. When assessing toxicological data, 10 percent extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint. Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, USEPA, 2012).

For the specific context of setting an MCLG for perchlorate, the EPA made a policy decision to evaluate the level of perchlorate in water associated with a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in population IQ. The EPA selected IQ as a

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surrogate for neurodevelopmental effects based upon its evaluation of the epidemiologic literature describe above. The need to utilize the best available peer reviewed data to inform scientific assumptions and policy choices to meet the statutory requirements associated with developing an MCLG under the SDWA highlights the challenges associated with regulating chemicals for which potential effects are indirect, and scientific data do not address all uncertainties. Sometimes as in this case, the Agency must make a policy decision as to what effect is adverse when science does not provide a clear threshold. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants for which there is concern about potential thyroid effects, either under the SDWA or other statutory frameworks.

Applying these response rates to the results from the reanalysis of Korevaar et al., (2016), results in a POD dose of 3.1 µg/kg/day for a 1 percent decrease in the population's IQ, a POD dose of 6.7 µg/kg/day for a 2 percent decrease in the population's IQ, and a POD dose of 10.8 µg/kg/day for a 3 percent decrease in the population's IQ. These PODs associated with a 1, 2, or 3 percent decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the POD is designed to provide an adequate margin of safety for the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 µg/day and a TSH feedback loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the methodological reasons described previously, the EPA believes that the selection of these parameters and this

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point of departure assures no known or anticipated adverse effects on the health of the most sensitive population and allows for an adequate margin of safety.

I. Translate PODs to RfDs

When deriving an RfD the EPA evaluates whether to apply uncertainty/variability factors to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002). As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a no-observed-adverse-effect-level (NOAEL), and an incomplete database. The factors are intended to account for: 1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); 2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); 3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); 4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and 5) uncertainty associated with extrapolation when the database is incomplete. (U.S. EPA, 2011b) The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., uncertainty factor (UF) for within-human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. The approach taken to derive the RfD attempts to address variability between the general population

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and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.

Further, as discussed in section III.C. of this notice the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. In addition, this analysis is

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[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the MCLG Approaches Report.

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assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is potentially because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et al., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the fetal thyroid begins secreting thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels available to the fetus. Given that the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. Therefore, as described above, the EPA selected an intraspecies UF of 3 to account for the uncertainties in modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children.

The EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF)

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for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. As noted above, the Agency has opted to apply a UF of 3 to the POD, which adds an adequate margin of safety to the MCLG derivation. Section 4.4.5.3 (p 4-42) of *A Review of the RfD & RfC Processes* recommends reducing the intraspecies UF from a default of 10 "only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)" (p. xviii, USEPA, 2002).The EPA selected a UF of 3 instead of the full 10 because the modeled groups within the population that are identified as likely to be at greater risk to perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother) and has selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake).

Below we list the other uncertainty factors added and the justification.

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.
- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

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occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.

- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.
- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).
- The product of all the uncertainty factors (UF_H) is 3 (3 x 1 x 1 x 1 x 1).

Below we generate RfD's for each of the points of departure.

Using the POD of 6.7 µg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.2\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 µg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.0\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

J. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\ \left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 µg/kg/day for a 1 percent decrease in IQ, 2.23 µg/kg/day for a 2 percent decrease in IQ, or 3.6 µg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution of drinking water to overall perchlorate exposure.

To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate specific to women of childbearing age (i.e., non-pregnant, non-

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lactating, 15–44 years of age (0.032 L/kg/day). This decision is consistent with the analysis used in deriving an RSC, which was performed using food consumption information for a population of women of childbearing age from NHANES. The 90th percentile is chosen to account for variability in drinking water ingestion rates, but also adds another layer of health protection for 90% of women (Table III-3).

The EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable. The use of the drinking water intake for 15-44 year old women is consistent with the analysis used in deriving an RSC_W (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the EPA's Exposure Factors Handbook (USEPA, 2011c) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis.

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Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2019c). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and

- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in about 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (μg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The details of these assumptions are explained on page 5-5 of the Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (USEPA 2019c). Specifically, the EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the 20 samples included in the TDS data. In order to estimate the 95th percentile from the 20 samples, the EPA used the second-highest test result for each food to represent the 95th percentile concentration. While simple, this method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine [ADDIN EN.CITE <EndNote><Cite><Author>Carriquiry</Author><Year>2016</Year><RecNum>2008</RecNum><DisplayText>(Carriquiry et al., 2016)</DisplayText><record><rec-number>2008</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039524">2008</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carriquiry, A. L.

</author><author>Spungen, J. H.</author><author>Murphy, S. P.</author><author>Pehrsson, P. R.</author><author>Dwyer, J. T.</author><author>Juan, W.</author><author>Wirtz, M. S. </author></authors></contributors><titles><title>Variation in the iodine concentrations of foods: considerations for dietary assessment</title><secondary-title>The American Journal of Clinical Nutrition</secondary-title></titles><periodical><full-title>The American Journal of Clinical Nutrition</full-title></periodical><pages>877S–887S</pages><volume>104</volume><number>Suppl 3</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. The aforementioned method for identifying the 95th percentile concentration of perchlorate from food was selected over other, more "statistically based" methods for estimating percentiles as it avoids the need to assume a distributional shape for the samples. The EPA determined that it was more reliable to assume the empirically derived distribution as the basis for selecting the 95th percentile (i.e., assuming the distribution was equal to the distribution of samples collected in the TDS), as opposed to forcing a distributional shape, such as normal or log-normal, onto the data that may not necessarily be appropriate. With the chosen method, we can at least be sure that the distributional shape is appropriate for the data at hand, whereas by choosing the alternative that assumes a distributional shape, in many instances we would not even be certain of that. The EPA used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate

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concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 µg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile perchlorate food concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

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Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

The EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III-5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using the EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.0	56%	0.032	18
2.2	80%	0.032	56
3.6	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss or a 2-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

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$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the NPDWR. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 µg/L based on the rationale and methodology described in Section III above. The derivation of the proposed MCLG uses a point of departure based upon a two percent decrease in IQ for offspring of hypothyroxinemic women of child bearing age have with low iodine intake. The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the subpopulation of interest.

As described in Section III, the EPA has selected model parameters and other factors for the derivation of the MCLG that are health protective, including the focus on the most sensitive life stage. The EPA believes that the selection of the combination of protective parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive subpopulation and allows for an adequate margin of safety. The EPA also acknowledges the uncertainties in the derivation of the proposed (and alternative) MCLGs. The EPA acknowledges in particular the challenge associated with selecting the decrement of IQ that

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represents an adverse effect at the population level and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement given the absence of robust human epidemiological data directly linking perchlorate exposure to IQ decrements. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2019b). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018c). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

Because the EPA is taking comment on alternative MCLG values of 18 µg/L and 90 µg/L the Agency evaluated the feasibility of setting an MCL at these levels. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this

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level under field conditions (USEPA 2018a, 2019b). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed

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science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA Section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The UCMR 1 is the primary source of occurrence data the EPA relied on to estimate the number of water systems (and associated population) expected to be exposed at levels of perchlorate which could potentially exceed the proposed and alternative MCL levels. Since UCMR 1 data was first used to inform the Agency actions on the 2008 preliminary regulatory determination and the 2011 final regulatory determination, the Agency has modified its analysis of the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions at some States that have enacted perchlorate regulations since the UCMR 1 data was collected. Despite these updates, the EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants

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(USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to the EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 μg/L for perchlorate in the UCMR.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

In September of 2012, the EPA received a "Request for Correction" letter from the United States Chamber of Commerce regarding information and data (i.e., the occurrence of perchlorate in drinking water) used by the EPA in its 2011 determination to regulate perchlorate. The U.S. Chamber of Commerce letter stated that the EPA relied upon: 1) data that did not comply with data quality guidelines and 2) data that was not representative of current conditions.

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In response[12] to the U.S. Chamber of Commerce, the EPA conducted a detailed assessment of the source water sample detections and determined that it was most appropriate to exclude the source water sample detections from the UCMR 1 perchlorate data set when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 perchlorate data set. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 perchlorate data set. As a result of the assessment, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the entry point to the distribution system. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections from 149 PWSs.

Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

In response to the U.S. Chamber of Commerce request, the EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two states. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION

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[12] See the EPA response letter at https://www.epa.gov/sites/production/files/2017-08/documents/12004-response_0.pdf

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{"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states are now required to

keep perchlorate levels in drinking water below their state limits, which are lower than the proposed MCL and alternative MCLs. Therefore, the UCMR 1 sampling results from systems in these states do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. The notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

To update the occurrence data for systems sampled during UCMR 1 from the States of California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

Out of the 540 detections previously described the EPA updated data for 321 detections (320 from California systems and 1 from a Massachusetts system). The convention used by the EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported compliance monitoring data, if more than one

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data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were the EPA could not find updated entry point data, then the original data from UCMR 1 for such entry point was kept.

Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 µg/L	15	525	540
Sample measurements > 18 µg/L	1	16	17
Sample measurements > 56 µg/L	0	2	2
Sample measurements > 90 µg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 µg/L	8	328	336
Entry points at which measurements > 18 µg/L	1	16	17
Entry points at which measurements > 56 µg/L	0	2	2
Entry points at which measurements > 90 µg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 µg/L	8	141	149
Systems at which measurements > 18 µg/L	1	14	15
Systems at which measurements > 56 µg/L	0	2	2
Systems at which measurements > 90 µg/L	0	1	1

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UAoGFPZv","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The total row counts and counts of measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population

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is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements > 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements > 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements > 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ChxDKgDr","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting

level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCLs. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"adhRbcXq","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In summary, the perchlorate occurrence information suggests that at an MCL of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. One of these two systems would exceed the alternative MCL of 90 µg/L. In addition, at an MCL of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is ''feasible'', the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, the SDWA directs the EPA to determine that it is economically and technologically feasible to

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ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain ''criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels.'' (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report (USEPA, 2019b).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of sample analysis and data reporting. All of the proposed EPA analytical methods provide

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performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

The EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework set out in 40 CFR 141 Subpart C (Standardized Monitoring Framework). Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. The EPA is proposing that consistent with the standardized monitoring framework water systems would be initially required to monitor quarterly for perchlorate. The EPA is also proposing that based upon the monitoring results States would be able to reduce the monitoring frequency to annually, once every three years or once every nine years if the State concludes that the system is reliably and consistently below the MCL. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point in the next quarter after the violation occurred (40 CFR 141.23(c)(7)). The state may allow the system to return to the reduced monitoring frequency when the state determines that the system is reliably and consistently below the MCL. However, the state cannot make a determination that the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples below the MCL have been collected (40 CFR

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141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the state (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under this proposal, water systems may apply to the state, and states may grant, a 9-year monitoring waiver for perchlorate if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A state may grant a waiver for surface water systems after three rounds of annual monitoring with results less than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

Under this proposal, violations of the perchlorate MCL would be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the perchlorate MCL would be determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than

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10,000 persons must collect 4 quarterly samples for perchlorate during the second compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the Standardized Monitoring Framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the third compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the Standardized Monitoring Framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered perchlorate data collected after January 1, 2020 to satisfy the initial monitoring requirements. To satisfy initial perchlorate monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022 for CWSs serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for NTNCWs and for CWSs serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

A community water system must prepare and deliver to its customers an annual Consumer Confidence Report (CCR) in accordance with requirements in 40 CFR 141 Subpart O. A CCR provides customers with information about their local drinking water quality as well as information regarding the water system compliance with drinking water regulations. Under this proposal CWSs would be required to report perchlorate information in their CCR.

B. What are the Public Notification Requirements?

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All public water systems must give the public notice for all violations of NPDWRs and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, per 40 CFR 141.202(b)(1), notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation under this proposal.

X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by states to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in states issuing small system variances under Section 1412(e) of the SDWA.

The Agency solicits public comment on the choice of available treatment technologies discussed in this section.

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A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal

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efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"s9dVZckb","properties":{"formattedCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","plainCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","noteIndex":0},"citationItems":[{"id":1048,"uris":["http://zotero.org/groups/945096/items/KIPNEQUM"],"uri":["http://zotero.org/groups/945096/items/KIPNEQUM"],"itemData":{"id":1048,"type":"paper-conference","title":"Castaic Lake Water Agency Operating Experience with Lead-Lag Anion Exchange for Perchlorate Removal","container-title":"Proceedings of the American Water Works Association Water Quality Technology Conference","event":"Water Quality Technology Conference","author":[{"family":"Drago","given":"J.A."},{"family":"Leserman","given":"J.R."}],"issued":{"date-parts":[["2011",11]]}}},{"id":1154,"uris":["http://zotero.org/groups/945096/items/2DBS6UYD"],"uri":["http://zotero.org/groups/945096/items/2DBS6UYD"],"itemData":{"id":1154,"type":"article","title":"News: Ion=Exchange System Removes Perchlorate","publisher":"Membrane Technology","author":[{"literal":"Membrane Technology"}],"issued":{"date-parts":[["2006",4]]}}},{"id":1125,"uris":["http://zotero.org/groups/945096/items/6WYYWFY2"],"uri":["http://zotero.org/groups/945096/items/6WYYWFY2"],"itemData":{"id":1125,"type":"re

port","title":"Case Study: Municipality in the State of Massachusetts","author":[{"literal":"Siemens Water Technologies"}],"issued":{"date-parts":[["2009"]]}}},{"id":1118,"uris":["http://zotero.org/groups/945096/items/5PV8GPIA"],"uri":["http://zotero.org/groups/945096/items/5PV8GPIA"],"itemData":{"id":1118,"type":"article","title":"Technical/Regulatory Guidance: Remediation Technologies for Perchlorate Contamination in Water and Soil","URL":"http://www.eosremediation.com/download/Perchlorate/ITRC%20PERC-2.pdf","author":[{"literal":"The Interstate Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, i.e., the contaminant "breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on

studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cxQjBTo8","properties":{"formattedCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","plainCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}

],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed (i.e., operated on a 'throw-away' basis). This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"I0SaZZiL","properties":{"formattedCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/item

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s/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"dat

e-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Ion exchange can increase the corrosivity of treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dcLyBjzj","properties":{"formattedCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","plainCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":1079,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":1079,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1078,"uris":["http://zotero.org/groups/945096/items/BNWD5VQP"],"uri":["http://zotero.org/groups/945096/items/BNWD5VQP"],"itemData":{"id":1078,"type":"article-journal","title":"Rotation ion-exchange system removes perchlorate","page":"454A-455A","volume":"32","journalAbbreviation":"Environ. Sci. Technol.","author":[{"family":"Betts","given":"K.S."}],"issued":{"date-parts":[["1998"]]}}},{"id":1208,"uris":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"uri":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"itemData":{"id":1208,"type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}] because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench-scale tests and full-scale treatment plant studies [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CnYkqct9","properties":{"formattedCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1019,"uris":["http://zotero.org/groups/945096/items/E5WRR4HD"],"uri":["http://zotero.org/groups/945096/items/E5WRR4HD"],"itemData":{"id":1019,"type":"article-journal","title":"Evaluation of electron donors for biological perchlorate removal highlights the importance of diverse perchlorate-reducing populations","container-title":"Environmental Science: Water Research & Technology","page":"1049-1063","volume":"2","author":[{"family":"Kotlarz","given":"N."},{"family":"Upadhyaya","given":"G."},{"family":"Togna","given":"P."},{"family":"Raskin","given":"L."}],"issued":{"date-

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parts":[["2016"]]}}},{"id":1106,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1106,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR, respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 μg/L ClO4–. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 μg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-parts":[["2015",12,1]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"

],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}},{"id":1093,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1093,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and

Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nKwIqjde","properties":{"formattedCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/

BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ISPg08cl","properties":{"formattedCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","plainCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","noteIndex":0},"citationItems":[{"id":1047,"uris":["http://zotero.org/groups/945096/items/X3WWHCXS"],"uri":["http://zotero.org/groups/945096/items/X3WWHCXS"],"itemData":{"id":1047,"type":"speech","title":"The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher-place":"U.S. Environmental Protection Agency,

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Office of Research and Development, National Risk Management Research Laboratory","event-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1046,"uris":["http://zotero.org/groups/945096/items/IIXUW45F"],"uri":["http://zotero.org/groups/945096/items/IIXUW45F"],"itemData":{"id":1046,"type":"article","title":"Supporting data for presentation: The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1045,"uris":["http://zotero.org/groups/945096/items/FLVLSXCS"],"uri":["http://zotero.org/groups/945096/items/FLVLSXCS"],"itemData":{"id":1045,"type":"speech","title":"The Impact of Temperature on Anaerobic Biological Perchlorate Treatment","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dugan","given":"N.R."},{"family":"Williams","given":"D.J."},{"family":"Meyer","given":"M."},{"family":"Schneider","given":"R.R."},{"family":"Speth","given":"T.F."},{"family":"Metz","given":"D.H."}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in

bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"NDoHjLOr","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"

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report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"f4qlOob5","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","noteIndex":0},"citationItems":[{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security

Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ySKwU3Em","properties":{"formattedCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1051,"uris":["http://zotero.org/groups/945096/items/Z7PC3BME"],"uri":["http://zotero.org/groups/945096/items/Z7PC3BME"],"itemData":{"id":1051,"type":"speech","title":"Full-Scale Biological Denitrification Plants in Germany, Austria and Poland","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dordelmann","given":"O."}],"issued":{"date-parts":[["2009",11]]}}},{"id":1026,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1026,"type":"rep

ort","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litch

field","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"edXX3GgQ","properties":{"formattedCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, &

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Her, 2005)","plainCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":985,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-parts":[["1998"]]}}},{"id":986,"uris":["http://zotero.org/groups/945096/items/YHEV76YW"],"uri":["http://zotero.org/groups/945096/items/YHEV76YW"],"itemData":{"id":986,"type":"paper-conference","title":"Perchlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher-place":"Phoenix, AZ","event":"American Water Works Association Membrane Technology Conference","event-place":"Phoenix, AZ","author":[{"family":"Nam","given":"S."},{"family":"Kim","given":"S."},{"family":"Choi","given":"H."},{"family":"Yoon","given":""},{"family":"Silverstein","given":"J."},{"family":"Amy","given":"G."}],"issued":{"date-parts":[["2005"]]}}},{"id":992,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":992,"type":"article-

journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":991,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water.

Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in [REF _Ref529958951 \h]. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"J9AlL73G","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table X-[SEQ Table * ARABIC \s 1]: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, the EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

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The SSCT listed in [REF _Ref529958951 \h] include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LHgBHn5b","properties":{"formattedCitation":"(USEPA, 1998)","plainCitation":"(USEPA,

1998)","noteIndex":0},"citationItems":[{"id":1215,"uris":["http://zotero.org/groups/945096/items/399QNBY4"],"uri":["http://zotero.org/groups/945096/items/399QNBY4"],"itemData":{"id":1215,"type":"article","title":"Variance Technology Findings for Contaminants Regulated Before 1996","publisher":"EPA 815–R– 98–003. September","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of median household income. [REF _Ref529959037 \h] shows the expenditure margins derived for the analysis. These margins show the cap on affordable incremental annual expenditures.

Table X-[SEQ Table * ARABIC \s 1]: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2scXqyv0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"x096Tc8Y","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1225,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1225,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Rg9m81J","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018b)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018b)","noteIndex":0},"citationItems":[{"id":1226,"uris":["http://zotero.org/groups/945096/items/GTI7H6YK"],"uri":["http://zotero.org/groups/945096/items/GTI7H6YK"],"itemData":{"id":1226,"type":"article","title":"CPI--All Urban Consumers (all items), for areas under 50,000 persons","author":[{"family":"Bureau of Labor Statistics (BLS)","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
b. Affordability threshold equals 2.5 percent of MHI.
c. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fS2Ibu6t","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":163,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":163,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[REF _Ref529959069 \h] shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z6GYvRh1","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance

Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"18aKvRLD","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":147,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":147,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-[SEQ Table * ARABIC \s 1]: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8y1WSJT4","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.
a. For perchlorate, the EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA Sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

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40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance

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of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant. However, the perchlorate MCL could result in a greater frequency of reporting by certain states. See discussion of Paperwork Reduction Act compliance in Section XVI for more information.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);

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- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);
- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If the EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the

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monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B below summarizes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section C below summarizes this method used to estimate these benefits.

Section D below provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a), which is available in the docket for the proposed rule. Section XIII summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

Some costs associated with an NPDWR are incurred by all CWS and NTNCWS (e.g. monitoring and reporting) while others are only incurred by systems with perchlorate levels exceeding the MCL. The EPA estimated costs for CWS and NTNCWS to monitor and report perchlorate levels and also estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment because it is the most cost-effective treatment option and easy to operate on a 'throw-away' basis. If site-specific

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nontreatment options are available and lower cost, then this assumption might overstate costs. The EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring, report results, and apply for waivers. For the purpose of these estimates, the EPA assumed that both small and large systems would require the same amount of time to read the rule, apply for a waiver, and collect a water sample but that it would take large systems twice as long to provide initial training to their staff. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.
1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

Systems will incur monitoring costs over the analysis period. The EPA estimated monitoring frequency based on the proposed initial monitoring requirements, the standard monitoring framework requirements for inorganic contaminants, and the proposed

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implementation schedule. The estimated number of monitoring samples over the analysis period shown in Table XII-2 reflect the following phases:

1. Initial monitoring; four quarterly samples at every CWS and NTNCWS entry point.

2. Preliminary regular monitoring before waiver application: three regular monitoring samples for every CWS and NTNCWS entry point (collected annually at surface water system entry points and triennially at ground water system entry points).

3. Long-term monitoring at either (a) regular monitoring frequency for entry points at systems not granted waivers (60% of surface water system and 10% of ground water systems), or (b) reduced monitoring frequency for entry points at systems receiving waivers from primacy agencies (40% of surface water systems and 90% of ground water systems), which is one sample during every nine-year compliance monitoring cycle.

Table XII-2: Estimates of Compliance Monitoring Samples by Phase and System Type, Size, and Source Water

Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
1. Initial monitoring (4 quarterly samples in one year)	All CWS and NTNCWS	92,656	370,624
2. Preliminary regular monitoring (3 annual entry point samples for surface water systems and 3 triennial entry point samples for ground water systems)	All CWS and NTNCWS	92,654	277,962
3a. Long-term monitoring, no waiver (annual entry point samples)	60% of large surface water CWS	3,324	86,424
	60% of small surface water CWS and all surface water NTNCWS	6,064	139,472
3a. Long-term monitoring, no waiver (triennial entry point samples)	10% of large ground water CWS	680	4,080
	10% of small ground water CWS and all ground water NTNCWS	7,021	35,105
3b. Long-term monitoring, waiver (1 sample every 9 years)	40% of large surface water CWS	2,216	4,432
	40% of small surface water CWS and all surface water NTNCWS	4,043	8,086

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Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
3b. Long-term monitoring, waiver (1 sample every 9 years)	90% of large ground water CWS	6,117	12,234
	90% of small ground water CWS and all ground water NTNCWS	63,189	63,189

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780).

1. The EPA estimated a total of 92,656 entry points based on the total number of potentially affected systems in SDWIS/FED and the average number of entry points per system in the UCMR 1 data by size category and source water. The initial monitoring phase includes all entry points. The EPA assumed that the two entry points with MCL exceedances at the proposed MCL of 56 µg/L would continue to take quarterly samples for the duration of the analysis period, for a total of 232 samples. Thus, they are excluded from the estimates for the subsequent phases of regular and long-term monitoring. Primacy agencies may, however, allow monitoring to return to a regular schedule if treatment process operation can reliably and consistently reduce perchlorate below the MCL.

2. For Phase 3, the estimate of aggregate samples is the product of the number of entry points and the frequency of sampling during the remaining years of the analysis period. For example, large surface water CWS without a waiver conduct long-term annual monitoring for 26 years because they complete preliminary regular monitoring in year 9. In contrast, large ground water CWS without a waiver begin long-term triennial monitoring in year 16 because their preliminary regular monitoring phase lasts for 9 years (3 triennial samples) instead of 3 years (3 annual samples). The estimates also reflect schedule differences by size because large CWS begin monitoring schedules three years earlier than small CWS and all NTNCWS.

To estimate costs to CWSs and NTNCWSs associated with time spent on compliance monitoring and other administrative costs, the EPA generally uses the labor rate[13] for full-time treatment plant operators in CWSs from USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5g8IJ6Eh","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/FHCVS

[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

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MRC"],"uri":["http://zotero.org/groups/945096/items/FHCVSMRC"],"itemData":{"id":992,"type":"article","title":"Labor Cost for National Drinking Water Rules","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2011"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of system entry points that exceed the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[14]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and

[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c) contains more complete discussion of the WBS models and the cost estimating approach.

nontreatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, the EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and

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untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 μg/L the blending target would be 45 μg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and Agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-3 summarizes the labor hour assumptions for these activities. The EPA requests comments on these assumptions.

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Table XII-3: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)
1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.
2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"C1A8zUkj","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","plainCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"uri":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"itemData":{"id":984,"type":"webpage","title":"Employer Cost for Employee Compensation -- September 2016","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2016"]]}},"label":"book","suffix":"Table 3"}],"schema":"https://github.com/citation-

style-language/schema/raw/master/csl-citation.json"}], for a fully loaded hourly wage rate for States of $50.67. The EPA requests comments on these labor rate assumptions.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mnzEXxZK","properties":{"formattedCitation":"(USEPA, 2008b)","plainCitation":"(USEPA, 2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":998,"uris":["http://zotero.org/groups/945096/items/QSXYHBID"],"uri":["http://zotero.org/groups/945096/items/QSXYHBID"],

"itemData":{"id":998,"type":"article","title":"Draft Information Collection Request for the Disinfectants/Disinfection Byproducts, Chemical, and Radionuclides Rule","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2008",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

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Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[15]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Q6RKolIZ","properties":{"formattedCitation":"(U.S. Census Bureau, 2017b)","plainCitation":"(U.S. Census Bureau, 2017b)","noteIndex":0},"citationItems":[{"id":1000,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":1000,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA divided the total annual system-level costs by the number of households served by the system.

C. Method for Estimating Benefits

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of

[15] For systems with monitoring costs only, household-level costs will be negligible.

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perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rCNbGglo","properties":{"formattedCitation":"(U.S. Census Bureau, 2017a)","plainCitation":"(U.S. Census Bureau, 2017a)","noteIndex":0},"citationItems":[{"id":189,"uris":["http://zotero.org/groups/945096/item

s/ZM7S6H44"],"uri":["http://zotero.org/groups/945096/items/ZM7S6H44"],"itemData":{"id":189,"type":"article","title":"Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016.","URL":"https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html#ds","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7XfZyKhY","properties":{"formattedCitation":"(Martin, Hamilton, & Osterman, 2017)","plainCitation":"(Martin, Hamilton, & Osterman, 2017)","noteIndex":0},"citationItems":[{"id":186,"uris":["http://zotero.org/groups/945096/items/MY6LPDKD"],"uri":["http://zotero.org/groups/945096/items/MY6LPDKD"],"itemData":{"id":186,"type":"article","title":"Births in the United States, 2016. NCHS Data Brief No. 287","URL":"https://www.cdc.gov/nchs/data/databriefs/db287.pdf","author":[{"family":"Martin","given":"J.A."},{"family":"Hamilton","given":"B.E."},{"family":"Osterman","given":"M.J.K"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 µg/L and alternative MCLs of 18 µg/L and 90 µg/L. The first step relates

changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake. For the BBDR simulations, the EPA used the 90th ingestion rate to be consistent with the MCLG modeling approach, which may overstate the exposure in the simulation.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"iqyVRL6z","properties":{"formattedCitation":"(Korevaar et al., 2016)","plainCitation":"(Korevaar et al., 2016)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of

low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt

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hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] study data. Ultimately, the changes in IQ are

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estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-4 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

Table XII-4: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2019a).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants that target the thyroid, such as

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nitrate, as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XIII provides additional discussion of uncertainties in this analysis.

D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 µg/L, Table XII-5 summarizes the total estimated cost of the proposed rule to water systems and primacy agencies, and Table XII-6 summarizes the estimated per-household cost for the system incurring treatment costs[16]. Table XII-7 summarizes the estimated benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

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Table XII-5: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

Source: [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-6: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA,

2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"

uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health

Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water

Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-

parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table XII-7: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

For the alternative MCL of 18 µg/L, Table XII-8 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-9 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-10 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

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Table XII-8: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H6Rcd4Hf","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Detail may not sum to total because of independent rounding.

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.

2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-9: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"uu13kmuC","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

Table XII-10: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EN9pibZj","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-11 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-12 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-13

summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

Table XII-11: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-12: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 µg/L because treatment costs to meet an MCL of 90 µg/L are lower than the costs to meet an MCL of 56 µg/L.

Table XII-13: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Table XII-14 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between an MCL of 56 µg/L and an MCL of 18 µg/L and between an MCL of 90 µg/L and 56 µg/L.

Section 1412(b)(4)(C) of the SDWA requires that when proposing a national primary drinking water regulation, "the Administrator shall publish a determination as to whether the benefits of the maximum contaminant level justify, or do not justify, the costs." The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative

cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 µg/L using the best available science and data, the EPA Administrator has determined based upon the available information that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs.

Under these circumstances, Section 1412(b)(6)(A) of the SDWA provides, with exceptions not relevant here, that "the Administrator *may*, after notice and opportunity for public comment promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits." The EPA has evaluated the benefits and costs of alternative MCL values of 18 µg/L and 90 µg/L. However, based upon the available information the Administrator also finds that the benefits of an NPDWR at the alternative MCL values would not justify the resulting rule costs. The alternative MCLs would not increase net benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar. Consistent with the discretion afforded the Agency by SDWA Section 1412(b)(6)(A) to decide whether or not to adjust an MCL to a level where the benefits justify the costs, the EPA is however proposing, and may finalize, the MCL of 56 µg/L notwithstanding the Agency's determination that benefits would not justify the costs.

Table XII-14: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05

Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E0mmmXDK","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA has presented an extensive discussion of the uncertainties in the key analyses informing this proposal in the uncertainty section of the MCLG Approaches Report and the uncertainties section of the Economic Analysis document (*USEPA, 2018b; USEPA, 2019a)*. A summarized description of these uncertainties are presented below.

A. Uncertainty in the MCLG Derivation

Each input into the analysis to inform the MCLG is a decision point associated with uncertainty. There is uncertainty in different aspects of the BBDR model, ranging from structural and functional relationships to specific parameter values for early pregnancy. There are very few data available to calibrate the pharmacokinetic aspects of the model, particularly at the life stage of interest. Also, the BBDR model does not explicitly consider the effect of the presence of other

goitrogens (e.g. thiocyanate, nitrate) or effects of thyroid disease states. Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. Additional uncertainty is introduced by linking the BBDR model estimates of maternal fT4 to altered neurodevelopment in offspring. None of the studies used to evaluate potential adverse neurodevelopmental outcomes in offspring born to hypothyroxinemic mothers was performed in the U.S. None of the studies measured perchlorate exposure. Not all the studies measured iodide levels in the study populations. The state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. There are numerous indices used to assess neurodevelopmental impacts and there is some uncertainty regarding the selection of IQ as the critical endpoint for setting the MCLG.

A recently published paper evaluating the EPA's BBDR model and MCLG Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al., 2019).

B. Uncertainty in the Economic Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2019a). Table XIII-1 provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

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Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect
Baseline Occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water).	± (benefits and costs will change in the same direction)
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 µg/L or 90 µg/L and that one small system would exceed 18 µg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than the MCLs that are not captured in the national extrapolation results.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum.	± (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4.	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The EPA used a 90th percentile water intake rate to derive the MCLG and the dose-response equations for the benefits analysis. This approach results in a protective MCLG value, but may overstate intake for the benefits analysis.	+ (benefits only)
The IQ valuation uses estimates that the EPA derived using the same approach as Salkever (1995). Results from other IQ valuation studies might result in higher or lower benefit estimates.	± (benefits only)
The benefits analysis is based on a single health endpoint and the value of the endpoint is based solely on lost earnings.	− (benefits only)
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)

Description	Potential effect
The EPA assumed that all entry points requiring treatment would implement ion exchange, which may overestimate costs if non-treatment is an option for one or more entry points or underestimate costs if site-specific conditions result in higher costs at one or more entry points.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	– (costs only)
The EPA assumed that 90% of ground water systems and 40% of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al. 1991; Pop et al. 1999; Pop et al. 2003; Kooistra et al. 2006)" (p. 10, SAB for the U.S. EPA, 2013). The EPA's literature review identified potential relationships between maternal thyroid hormone alterations and the risk of schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none

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of which are being currently quantified in this assessment. Other potentially omitted benefits include risks associated with effects of thyroid disorders in adults, including cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints are not monetized in this benefits analysis. The assumptions used to account for the previously mentioned variability of the BBDR model inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above may result in an overestimate of the monetized benefits. Because IQ is a surrogate for broad range of potential neurodevelopmental risks, it is unclear whether the analysis as a whole over- or under-estimates the monetized benefits of a reduction of perchlorate in drinking water.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues will be especially helpful to the EPA in developing a final rule. The EPA specifically requests comment on the following topics.

- The adequacy and uncertainties of the BBDR model developed by the EPA to predict thyroid hormone level changes caused by perchlorate exposure to pregnant women with low iodide intake, including the model and model parameters and assumptions (Section III and Approaches Report).

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- The adequacy and uncertainties of the EPA's review and application of the epidemiologic literature to quantify the relationship between thyroid hormone changes in pregnant women and neurodevelopmental effects including the assumptions, the selection of the approach used, and the study used (Section III and Approaches Report).
- The adequacy and uncertainties of the methodology to derive the MCLG including points of departure, assumptions, uncertainty factor, and relative source contribution (Section III and Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water).
- The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.
- The feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.
- The adequacy of the underlying assumptions and analysis of occurrence (Section VI).
- The costs and availability of Treatment Technologies (Section X).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate costs and describe unquantified costs including the estimates of monitoring frequency, likelihood of systems receiving a monitoring waiver, the administrative labor rate and the operator labor rate. (Section XII and the Health Risk Reduction Cost Analysis).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate benefits and describe unquantified benefits (Section XII and the Health Risk Reduction Cost Analysis).

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- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's finding in accordance with Section 1412(b)(4)(C) of the SDWA that the benefits of the proposed 56 µg/L MCL for perchlorate do not justify the costs, and the information that supports that determination as described in Section XII of this notice.
- The Administrator's proposal to, consistent with the discretion afforded him by SDWA Section 1412(b)(6)(A), adopt an MCL of 56 µg/L notwithstanding the Agency's SDWA Section 1412(b)(4)(C) determination that the benefits of the MCL would not justify its costs.
- The Agency's conclusion that no alternative MCL, including the alternative MCL values of 18 µg/L and 90 µg/L discussed above, would "maximize health risk reduction benefits at a cost that is justified by the benefits" and the information and analytical approaches used to arrive at that conclusion. The EPA is especially interested in comments suggesting other approaches to deriving an MCL for which the benefits justify the costs.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on several factors. First, the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), suggest that perchlorate does not occur in public water systems with a frequency and at levels of

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public health concern[17] and suggest that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate, but the available data indicates that very few would find it at levels of public health concern. Specifically, perchlorate occurrence information suggests that at an MCL of 56 µg/L only 2 systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Even at an MCL of 18 µg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. Only one system would exceed the alternative MCL of 90 µg/L.

The EPA notes that in 2008, the EPA stated in its preliminary regulatory determination that perchlorate did not occur with a frequency and at levels of public health concern in public water systems based upon the health effects and occurrence information available at that time, which indicated that 0.8% of public water system had perchlorate at levels exceeding the HRL of 15 µg/L. The EPA also stated that there was not a meaningful opportunity for a NPDWR to reduce health risks based upon the estimates at that time that 0.9 million people had perchlorate levels above the HRL.

The EPA further notes that the Agency has previously determined CCL1 and CCL2 contaminants did not occur with frequency at levels of public health concern when the percentage of water systems exceeding the HRL were greater than the frequency of perchlorate

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[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or 90 µg/L, which are the possible levels expected to cause adverse human health effects.

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occurrence level at the proposed MCL (0.004% of all water systems in the U.S.). For example, in 2003 the EPA determined that aldrin did not occur with a frequency and at levels of public health concern based upon data that showed 0.2% of water systems had aldrin at levels greater than the HRL. The EPA also concluded that there was not a meaningful opportunity for health risk reduction for persons served through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 1 million people (USEPA, 2003). In 2008 the EPA determined that DCPA Mono- and Di-Acid degradates did not occur with a frequency and at levels of public health concern based on data that showed 0.13% of water systems exceeded the HRL. The EPA also included that there was not a meaningful opportunity for health risk reduction through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 100,000 people (USEPA, 2008e).

SDWA Section 1412(b)(1)(A)(iii) states that the determination regarding the meaningful opportunity is "in the sole judgement of the Administrator" and therefore there may be other factors that contribute to this determination for any given contaminant.

If, after consideration of public comment, the EPA withdraws the perchlorate regulatory determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using its SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authorities, as appropriate.

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The EPA also requests comments on what guidance it could provide the public if the regulatory determination for perchlorate is withdrawn.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a)* is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in the EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

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The monitoring information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule including adopting the NPDWR into state regulations, providing training to state and PWS employees, updating their monitoring data systems, and reviewing system monitoring data and waiver requests. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) would not begin until after Year 3 due to the proposed effective date of this rule.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able

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to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to the EPA at the public docket established for this rule, which includes the ICR, Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996

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Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 7 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a). Table XII-1 and Table XII-2 show the annual compliance costs of the proposed rule on the small entities by system size for public and private systems, respectively. Based on a comparison of annual costs with annual revenue estimates, the EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2019a).

Table XII-1: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Public CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$224,248	$88 (0.04%)	$94 (0.04%)
Population served 101-500	$197,315	$88 (0.04%)	$94 (0.05%)

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Population served 501-3,300	$202,382	$88 (0.04%)	$94 (0.05%)
Population served 3,301-10,000	$1,092,187	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,16]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Revenues include all sources of revenue including water revenue, non-water revenue, and municipal transfers to water systems.

b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

Table XII-2: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Private CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$139,911	$88 (0.06%)	$94 (0.07%)
Population served 101-500	$351,974	$88 (0.03%)	$94 (0.03%)
Population served 501-3,300	$254,706	$88 (0.03%)	$94 (0.03%)
Population served 3,301-10,000	$951,692	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,16]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Revenues include all sources of revenue including water revenue and non-water revenue.
b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of Tribal officials early in the process of developing this proposed regulation to permit them to have

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meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a webinar with interested tribes on February 28, 2012 to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012a). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk

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reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2019a) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

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The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. The EPA methods 314.0, 314.1, 314.2, 331.0, and 332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such

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bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking

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Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC, 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (USEPA, 2012; NRC, 2005). On May 29, 2013, the EPA received significant input from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (USEPA, 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking process for perchlorate (USEPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (USEPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (USEPA 2013a).

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Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). The EPA provided information to HHS officials on the draft proposed perchlorate regulation and considered HHS input as part of the interagency review described in section XVII.A.

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List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew R. Wheeler,

Administrator.

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For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

   k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

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l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."

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8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."
9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b), 141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

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§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	**MCL (mg/l)**	**Methodology**	**Detection limit (mg/l)**
*******	*******	*******	*******
Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS])

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		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.000008 (Selected Ion Monitoring [SIM]) 0.00002
*******	*******	*******	*******

*****

*****

(c)***

(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023 and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must

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collect four consecutive quarterly samples at all sampling points between January 1, 2026 and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023 and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution system may use the monitoring data from the compliance monitoring period that began between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data

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from the compliance monitoring period between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in

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accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	**Methodology[13]**	**EPA**	**ASTM[3]**	**SM[4] (18th, 19th ed.)**	**SM[4] (20th ed.)**	**SM Online[22]**	**Other**
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed	314.1					

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	Conductivity Detection						
	Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	314.2					
	Liquid Chromatography Electrospray Ionization Mass Spectrometry	331.0					
	Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	332.0					

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******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

*****

[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower

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detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

Contaminant	Preservative[1]	Container[2]	Time[3]
*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the

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time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L
*******	*******

*****

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Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

*****

(b)***

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Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000

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persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	**Traditional MCL in mg/L**	**To convert for CCR, multiply by**	**MCL in CCR units**	**MCLG**	**Major sources in drinking water**	**Health effects language**
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						

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********	********	********	*******	*******	*******	*******
Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.

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*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation

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*******				
B. Inorganic Chemicals (IOCs)				
*******				
14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			

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C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

[2] MCL – Maximum contaminant level

PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

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b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	**BAT(s)**
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

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*****

14 = Biological Treatment

*****

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MEMORANDUM

SUBJECT: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (Tier 1 Action; SAN 5555; RIN 2040-AF28) – **ACTION MEMORANDUM**

FROM: David P. Ross
Assistant Administrator (4101M)

THRU: Office of Policy (1803A)
Office of Executive Secretariat (1105A)

TO: Andrew J. Wheeler
Administrator (1101A)

PURPOSE

Attached for your signature is a proposed rule, titled "National Primary Drinking Water Regulations: Proposed Perchlorate Rule." We recommend signature and publication of this notice to solicit public comment on the EPA's proposal to establish a national primary drinking water regulation (NPDWR) and a non-enforceable maximum contaminant level goal (MCLG) for perchlorate under the Safe Drinking Water Act (SDWA). The proposed NPDWR includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L (56 µg/L), which is proposed to be set at a level equal to the proposed MCLG. The EPA is seeking comment in the attached notice on whether the Agency should consider setting the perchlorate MCLG and MCL at alternative values of 0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). The EPA is also seeking comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water.

DEADINE/TIMELINE

In February 2011, the EPA published a final determination to regulate perchlorate in drinking water. Section 1412(b)(1)(A) of the SDWA requires that the EPA issue a proposed NPDWR within 24 months of the final regulatory determination and a final NPDWR within 18 months after the proposal. However, when the EPA consulted with the Science Advisory Board (SAB), the Agency received recommendations that the EPA prepare a pharmacokinetic model (i.e., a biologically based dose-response model [BBDR]) to predict the effects of perchlorate exposure on the thyroid function in pregnant women and their children, to develop the MCLG for perchlorate. The EPA collaborated with Food and Drug Administration scientists to perform the modeling recommended by the SAB and completed the analysis and associated peer reviews in March 2018.

In February 2016, the Natural Resources Defense Council (NRDC) filed a lawsuit for failure of the EPA to perform its mandatory duties of proposing and finalizing a regulation for perchlorate in accordance with timelines provided in the SDWA. The court-approved consent decree established deadlines for the EPA to sign a proposed rule by October 31, 2018, and a final rule by December 19, 2019.

The EPA was granted an extension on the consent decree for signature of the proposed rule until April 30, 2019. However, due to a partial government shutdown in early 2019, an additional extension was given for signature of the proposed rule until May 28, 2019. The EPA is addressing the consent decree requirements to sign a NPDWR and issue a MCLG for perchlorate in this proposed rule by May 28, 2019.

OVERVIEW

Perchlorate is an inorganic anion which occurs naturally. It is also manufactured as an oxidizer for rockets, missiles, and fireworks and can be an impurity in hypochlorite disinfectants. The public may be exposed to perchlorate through food and drinking water. When exposed, perchlorate interferes with the thyroid gland by inhibiting iodide uptake, which impacts the production of thyroid hormones that are crucial for normal growth and development. Poor iodide uptake in pregnant and lactating women is linked to delayed development and decreased learning capabilities in their infants.

The EPA proposes to establish a NPDWR and a MCLG and MCL of 0.056 micrograms per liter (mg/L) (56 ug/L) for perchlorate based on avoiding neurodevelopmental impacts in the most sensitive population, the children of pregnant women with low iodide intake. The standard is proposed at a level that will prevent these children from having intelligence quotient (IQ) decrements greater than 2 points and includes a margin of safety. The EPA proposes requirements for water systems to conduct monitoring and reporting on perchlorate, and to provide information on perchlorate levels to consumers. The EPA also proposes requirements for primacy agencies that implement the Public Water System Supervision program under the SDWA. The proposal includes a list of treatment technologies to enable water systems to comply with the MCL, including affordable technologies for small systems.

In the preamble to the proposed rule, the EPA presents the results of its economic analysis and the Agency's conclusion that the benefits of the proposed regulation do not justify the costs. The EPA seeks comment on whether the Agency should set the MCLG and MCL for perchlorate at alternative values of 0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). These alternatives would avoid IQ decrements of 1 or 3 points, respectively, in the most sensitive population and include a margin of safety. Finally, the EPA seeks comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water based on the new information that indicate perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Under this alternative, the EPA would not issue a final MCLG or NPDWR for perchlorate.

The EPA has determined that the National Primary Drinking Water Regulations: Proposed Perchlorate Rule does not have disproportionately high and adverse human health or environmental effects on minority populations, low-income populations and/or indigenous

peoples, as specified in Executive Order 12898 (59 FR 7629, February 16, 1994), which establishes federal executive policy on environmental justice. This action would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

ANTICIPATED PUBLIC STAKEHOLDER RESPONSE

The EPA expects a variety of reactions and responses from stakeholders. Public health and environmental groups may state that proposed regulation is not sufficiently protective and that the EPA does not have the authority to withdraw a determination to regulate a contaminant under the SDWA. These groups may claim that the regulatory process, established in the 1996 SDWA amendments, is not functioning as intended because the EPA has not yet regulated a contaminant identified through the Contaminant Candidate List and Regulatory Determinations processes. Some stakeholders may be critical of the scientific analysis used to inform the derivation of the perchlorate MCLG and the estimate of benefits from the proposed regulation. Industry groups, including the American Water Works Association, the Perchlorate Study Group, the American Chemistry Council, and the U.S. Chamber of Commerce may state that the models have too much uncertainty and variability to be used to establish a drinking water standard.

INTERNAL DEVELOPMENT AND REVIEW PROCESS

The EPA workgroup consists of representatives from the Office of Water, the Office of Children's Health Protection, the Office of General Counsel, the Office of Policy, the Office of Research and Development, the Office of Land and Emergency Management, and the Office of Chemical Safety and Pollution Prevention. The Office of Water sought review and input of the draft *Federal Register* notice from this workgroup prior to submission for interagency review.

INTERAGENCY REVIEW

The Office of Management and Budget (OMB) initiated review of the *Federal Register* notice: "National Primary Drinking Water Regulations: Proposed Perchlorate Rule" on April 15, 2019, and the EPA has addressed any comments made during the review. Edits made during OMB review are in the public docket.

IMPACTS

The EPA estimates this proposed rule would impose an annual cost burden between $9.7 and $10.3 million. Approximately $3.1 to $3.2 million of that annual cost will be borne by states (and the Navajo Tribe) that have primacy to oversee implementation of the requirements. Between $6.6 and $7.1 million of the annual cost will be borne by public water systems and their rate payers. Monitoring and administration requirements are the majority of the annual cost. The EPA estimates that very few systems will have to install or operate treatment to comply with the regulation.

The EPA determined that the proposed regulation will result in annual costs that are less than one percent of revenue for small public water systems affected by this proposed rule. The average annual costs range from $88 to $94 for these systems. The EPA determined that the compliance costs for this action in any given year are less than the threshold set in the Unfunded Mandates Reform Act ($100 million in expenditures to state, local, and tribal governments in aggregate or to the private sector).

PEER REVIEW
The OW followed the EPA peer review policy with respect to the underlying scientific BBDR model used to derive an MCLG for perchlorate in this regulatory action. As stated above, the EPA sought recommendations from the SAB for developing the proposed MCLG.

To ensure that the EPA had implemented the SAB recommendations, the Agency convened an independent peer review panel to evaluate the BBDR models in 2017. The EPA considered all the recommendations from the 2017 peer review and implemented those needed to increase the scientific rigor of the model and modeling results.

The EPA convened a second, independent peer review panel in 2018 to evaluate the updates to the BBDR model. The EPA also presented several approaches to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects, using evidence from the epidemiological literature. The January 2018 peer review concluded that "the current models are fit for purpose to determine an MCLG."

RECOMMENDATION
I recommend that you sign the attached rulemaking, "National Primary Drinking Water regulations: Proposed Perchlorate Rule."

Attachment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 22 2019

MEMORANDUM

OFFICE OF WATER

SUBJECT: National Primary Drinking Water Regulations: Proposed Perchlorate Rule

FROM: Anita M. Thompkins, Acting Director
Office of Ground Water and Drinking Water

TO: David P. Ross
Assistant Administrator

Attached for your approval and transmittal to the Office of the Administrator is a *Federal Register* notice titled: National Primary Drinking Water Regulations: Proposed Perchlorate Rule.

The EPA is proposing to establish a maximum contaminant level goal (MCLG) of 0.056 mg/L and a national primary drinking water regulation for perchlorate, which includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L, as authorized under the Safe Drinking Water Act (SDWA). The action includes proposed requirements for public water systems to conduct monitoring and reporting on perchlorate and to provide information on perchlorate levels to consumers. The proposal includes a list of treatment technologies to enable water systems to comply with the MCL, including affordable technologies for small systems. The EPA is also proposing requirements for primacy agencies that implement the Public Water System Supervision program under the SDWA.

The *Federal Register* notice presents the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. The proposal includes the EPA's request for comment on alternative MCL/MCLG values of 0.018 mg/L and 0.090 mg/L. Finally, the EPA seeks comment on whether the Agency should withdraw the 2011 determination to regulate perchlorate in drinking water based on the new information that indicate perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Under this alternative, the EPA would not issue a final MCLG or NPDWR for perchlorate.

I recommend that you approve the proposed rule and sign the Action Memorandum, transmitting the attached notice to the Office of the Administrator for signature. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

MEMORANDUM

SUBJECT: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (Tier 1 Action; SAN 5555; RIN 2040-AF28) – **ACTION MEMORANDUM**

FROM: David P. Ross
Assistant Administrator (4101M)

THRU: Office of Policy (1803A)
Office of Executive Secretariat (1105A)

TO: Andrew J. Wheeler
Administrator (1101A)

PURPOSE

Attached for your signature is a proposed rule, titled "National Primary Drinking Water Regulations: Proposed Perchlorate Rule." We recommend signature and publication of this notice to solicit public comment on the EPA's proposal to establish a national primary drinking water regulation (NPDWR) and a non-enforceable maximum contaminant level goal (MCLG) for perchlorate under the Safe Drinking Water Act (SDWA). The proposed NPDWR includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L (56 µg/L), which is proposed to be set at a level equal to the proposed MCLG. The EPA is seeking comment in the attached notice on whether the Agency should consider setting the perchlorate MCLG and MCL at alternative values of 0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). The EPA is also seeking comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water.

DEADINE/TIMELINE

In February 2011, the EPA published a final determination to regulate perchlorate in drinking water. Section 1412(b)(1)(A) of the SDWA requires that the EPA issue a proposed NPDWR within 24 months of the final regulatory determination and a final NPDWR within 18 months after the proposal. However, when the EPA consulted with the Science Advisory Board (SAB), the Agency received recommendations that the EPA prepare a pharmacokinetic model (i.e., a biologically based dose-response model [BBDR]) to predict the effects of perchlorate exposure on the thyroid function in pregnant women and their children, to develop the MCLG for perchlorate. The EPA collaborated with Food and Drug Administration scientists to perform the modeling recommended by the SAB and completed the analysis and associated peer reviews in March 2018.

CONCURRENCES

SYMBOL								
SURNAME								
DATE								

Cover Form and Checklist for *Federal Register* (FR) Document Submissions to the Office of Policy (OP)

Section 1: Tracking information

Contact name: Stephanie Flaharty Office/Region: OW

Contact phone and email: flaharty.stephanie@epa.gov; (202) 412-1702

Docket # *(if applicable)*: EPA-HQ-OW-2018-0780 FRL # *(if applicable)*:

SAN# *(if applicable)*: SAN 5555

Name of document: National Primary Drinking Water Regulations: Proposed Perchlorate Rule

Name of File: NPDWR for the Proposed Perchlorate Rule

Other Information (alternate contacts, etc.):

Is this action subject to the Congressional Review Act (CRA)?
For questions associated with the CRA, consult the attorney assigned to your action, or visit http://intranet.epa.gov/actiondp/documents/craguidance15-10-15.pdf.

Yes ☐ No ☑

Section 2: Requested Handling

You must select either Option 1 or Option 2.

☑ **Option 1: No Special Handling is Requested.** *Select this option if the special handling requests identified in Option 2 do not apply to your document. If you select this option, OP will submit your document to the OFR for publication without any special requests.*

☐ **Option 2: Special Handling is Requested.** *Select this option if one or more of the following apply to your document--and select all requests that apply.*

☐ **We need to SUBMIT to or PUBLISH in FR *by* or *on* a SPECIFIC DATE.** This document must be (choose one) Reason: (choose one)

Explain other:

This request is reserved to satisfy the requirements of court or meet the needs of senior policy officials. The FR team may ask for additional documentation. Before you request a modified schedule, please review our timetable at http://intranet.epa.gov/adplibrary/adp-milestones/fedreg.htm.

☐ **We need OFR to REVIEW and APPROVE the IBR contained in this rule.** The relevant IBR memo or letter and materials are attached.

☐ **We need to MANAGE the FR publication of multiple FR documents.** This document must (choose one) (choose one) the following FR document (choose one)

Title:

Docket # *(if applicable)*:

FRL *(if applicable)*: Published on *(if applicable)*:

☐ **We need OFR to confirm their receipt of this FR document:** Select this option ONLY if you need to ask OFR to provide a confirmation of receipt in order to document EPA's compliance with a legal requirement to submit the document to OFR by a specific date.

More information about FR Publication can be found on our website: **http://intranet.epa.gov/adplibrary/adp-milestones/fedreg.htm**

Section 3: Checklist for Document Format and Package Components

The following section provides formatting requirements for materials included in a submission package. Requirements are based on OFR's Document Drafting Handbook. Failure to adhere to these requirements could delay the publication of your document.

- [x] 1. EPA's Billing Code is present **(6560-50-P)** on original and each copy, on the first page of each document in the upper right corner.
- [x] 2. The **title** is concise, does not contain overly specific information, and does not contain legal citations.
- [x] 3. The **SUMMARY** section is no longer than one page.
- [x] 4. The **SUMMARY** section does not contain legal citations *(i.e., CFR citations, FR citations, USC citations, etc.).*
- [x] 5. The **DATES** section is labeled "**DATES**" *(Not "EFFECTIVE DATES", etc.).*
- [x] 6. The **Table of Contents**, if included, matches the headings in the preamble.

7. **Signature Block – Original Paper Version***
   - [x] a. The signature block contains a legible date.
   - [x] b. The signer's name and title are typed or printed under the signature line.
   - [x] c. *(if applicable)* "Acting" is added, in front of the title, if a person other than the official holder of that title is acting in that capacity. *(Note: no "for" is permitted in the signature block)*
   - [x] d. Any changes are initialed and dated. (*For example, corrections to make the typed or printed name match the signature are made by striking through the incorrect name, and initialiting and dating the correction.)*
   - [x] e. No White-Out or corrective tape is used on the signature page.

8. **Signature Block – Word File***
   - [x] a. The signature page matches items 7a – c above.
   - [x] b. The date is spelled out, with a period at the end. *(Example: "February 6, 2014.")*

- [x] 9. A rewritable CD **(CD-RW)** is included with the package. *(CD-R or DVD-RW are not acceptable)*

10. The CD-RW contains:
    - [x] a. the (1) **most recent Word version** of document that (2) **matches the original**, a scanned copy of
    - [x] b. the typesetting request form, and
    - [x] c. a scanned copy of the (signed) signature page.
    - [ ] d. Action Information Template for all EPA *Federal Register* publications, except NPRM, Direct Final and Final stages of Full SIP Approvals.

- [x] 11. The **original** document is **single-sided**, and each **copy** is **double-sided**.
- [x] 12. The correct number of copies are included. This number will depend on the type of document you are submitting. See FR publishing website, under "Submitting Packages to the FR Team".

Section 4: Certification and Signature

I certify that the CD-RW I am submitting as part of this package includes the **most recent Word file** of the document and matches the copies and the original included in this package.

5/22/19

Date/Signature of Contact Regarding Submitted Package

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 1/2/2020 6:42:59 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Revised Option Selection file
Attachments: Option Selection for Perchlorate 12-29-19v2.docx

Hi Eric,
Attached is the revised cost estimate for the "spring-in" option. Below are the assumptions used. I'll incorporate the new numbers in the version with Jennifer's comments.
Lisa

From: Khera, Rajiv <Khera.Rajiv@epa.gov>
Sent: Thursday, January 02, 2020 1:26 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Option Selection file

Hi Lisa-

The attached has the new estimates for Option 4 (see highlighted sections).

1. Split UMCR1 entry points into 4 groups:
UCMR1 nondetection group – 9-year monitoring only (**Nondetection** group)
UCMR1 detection group but max <= 9 ug/L – 9-year monitoring only (**Reliable** group)
UCMR1 detection max > 9 ug/L – SMF regular monitoring indefinitely (**Regular** group)
UCMR1 exceedance – SMF quarterly monitoring indefinitely (**Treatment** group; regardless of whether the systems need to report quarterly data, they will need to monitor perchlorate to ensure process effectiveness)

2. Split non-UCMR1 systems into 3 groups (net out UCMR1 entry points):
Nondetection group - initial monitoring and then 9-year monitoring; approximated as the entry points of systems in ~22 states that do not have either a UCMR1 or USGS (https://pubs.usgs.gov/ds/495/pdf/ds495.pdf) perchlorate detection.
Reliable group – initial monitoring and then 9-year monitoring); applied the 90% GW and 40% SW assumption to all non-UCMR1 entry points in states where perchlorate has been detected in either UCMR1 or USGS data; also generated outputs for percentages ranging from 50% to 100% to bound uncertainty.
Regular group – initial and regular SMF monitoring (annual for SW and triennial for GW); 10% of GW and 60% of SW.

3. Removed system waiver application costs (16 hours per system).

4. Kept state 'waiver' burden of 4 hours per system as a proxy for case-by-case assessment of small system vulnerability. Even states that have a blanket statewide waiver will incur some burden to develop and implement the new automatic waiver concept and other states may have more extensive data analysis requirements to determine which systems are eligible for automatic waivers even if they don't have system or entry point waiver requests to review.

Please feel free to call me at Ex. 6 Personal Privacy (PP) if you have any questions. Thanks
Rajiv

Message

From: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Sent: 6/28/2019 2:37:27 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Corr, Elizabeth [Corr.Elizabeth@epa.gov]
Subject: Published: Perchlorate Rule
Attachments: Perchlorate Proposed Rule.published 6 26 19.pdf

Good Morning Sam,

Please review the attached notice and let me know ASAP if you find any publication errors/typos.

Thanks,
Steph

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141 and 142

[EPA–HQ–OW–2018–0780; FRL–9994–68–OW]

RIN 2040–AF28

National Primary Drinking Water Regulations: Perchlorate

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

DATES: Comments must be received on or before August 26, 2019. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before July 26, 2019.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA–HQ–OW–2018–0780, at *https://www.regulations.gov*. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from *Regulations.gov*. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.*, on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit *http://www2.epa.gov/dockets/commenting-epa-dockets*.

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue NW, Washington, DC 20460; telephone number: (202) 564–1735; email address: *hernandez.samuel@epa.gov*.

SUPPLEMENTARY INFORMATION: In addition to the proposed regulation, the EPA is requesting comment on three alternatives: (1) Whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18 µg/L), (2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 µg/L), or (3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011, determination to regulate perchlorate in drinking water based on new information that indicates that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and there may not be a meaningful opportunity for health risk reduction through a drinking water regulation. Under this last alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate. This proposed rule is organized as follows:

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A. What is the EPA proposing?
B. Does this action apply to me?
II. Background
A. What is perchlorate?
B. Statutory Authority
C. Statutory Framework and Regulatory History
III. Assessment and Modeling of the Health Effects of Perchlorate
A. 2008 Preliminary Regulatory Determinations
B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination
C. Science Advisory Board Recommendations
D. Perchlorate Model Development and Peer Reviews
E. Sensitive Population for Deriving MCLG
F. BBDR Model Specification for the Sensitive Population
G. Epidemiological Literature
H. Identifying a Point of Departure for Developing the MCLG
I. Translate PODs to RfDs
J. Translate RfD Into an MCLG
IV. Maximum Contaminant Level Goal and Alternatives
V. Maximum Contaminant Level and Alternatives
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C. What are the State reporting requirements?
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B. Method for Estimating Costs
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A. Uncertainty in the MCLG Derivation
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XIV. Request for Comment on Proposed Rule
XV. Request for Comment on Potential Regulatory Determination Withdrawal
XVI. Statutory and Executive Order Reviews
A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review
B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs
C. Paperwork Reduction Act
D. Regulatory Flexibility Act (RFA)
E. Unfunded Mandates Reform Act
F. Executive Order 13132: Federalism
G. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments
H. Executive Order 13045: Protection of Children From Environmental Health and Safety Risks
I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use
J. National Technology Transfer and Advancement Act of 1995

K. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations
XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services
XVIII. References

I. General Information

A. What is the EPA proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of 56 µg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 µg/L.

The EPA is proposing an NPDWR for perchlorate in accordance with its February 11, 2011, (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: (1) The contaminant may have an adverse effect on the health of persons, (2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and (3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is soliciting comment on two alternative MCLG/MCL values of 18 µg/L and 90 µg/L respectively. Third, in light of new considerations that have come to the EPA's attention since it issued its positive regulatory determination in 2011, including information on lower levels of occurrence of perchlorate than the EPA had previously believed to exist and new analysis of the concentration that represents a level of health concern, this action also discusses and requests comment on an alternative action under which the EPA would withdraw its 2011 determination to regulate perchlorate. Under this alternative, there would be no MCLG or NPDWR for perchlorate.

B. Does this action apply to me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems: Non-transient, non-community water systems.
State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement.

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the **FOR FURTHER INFORMATION CONTACT** section.

II. Background

A. What is perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4^-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Statutory Framework and Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water system. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems (CWS) and non-transient, non-community water systems (NTNCWS). The UCMR collects data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556) which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999, 2000b).

The EPA and other federal agencies asked the National Research Council

(NRC) to evaluate the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide [1] into the thyroid by a protein molecule knows as the sodium/iodide symporter (NIS), which may lead to decreases in two hormones, thyroxine (T3) and triiodothyronine (T4) and increases in thyroid-stimulating hormone (TSH) (National Research Council (NRC), 2005b). Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the recommended National Research Council RfD of 0.7 µg/kg/day for perchlorate. The reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability (USEPA, 2005b).

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 µg/L based on the RfD of 0.7 µg/kg/day in making this conclusion (USEPA, 2008a). Based primarily on the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In January 2009 the EPA published an interim health advisory for perchlorate of 15 µg/L, consistent with the HRL derivation for perchlorate of 15 µg/L described above. Health Advisories are non-enforceable and non-regulatory and provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health Advisories provide the public, including the most sensitive populations, with a margin of protection from a lifetime of exposure. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information (74 FR 41883; USEPA, 2009a). After careful consideration of public comments on the October 2008 and August 2009 notices, on February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011a). The Agency stated then that when considering the alternative HRL benchmarks described in the 2009 notice, the likelihood of perchlorate to occur at levels of concern had significantly increased in comparison to the levels described on the 2008 preliminary negative determination. The EPA concluded that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally described in the 2008 notice.

In its 2011 determination, the Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data for systems in California and Massachusetts using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than October 31, 2018, and finalize an NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water was later extended to May 28, 2019. The consent decree is available in the docket for today's proposed rule.

III. Assessment and Modeling of the Health Effects of Perchlorate

Perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the NIS (ATSDR, 2008; Greer et al., 2002; NRC, 2005; SAB 2013; Taylor et al., 2013). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB for the U.S. EPA, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB for the U.S. EPA, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

The mode of action of perchlorate toxicity has been proposed as follows: exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland through the NIS (NRC, 2005; SAB for the U.S. EPA, 2013). A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that T3 and T4 require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased TSH, the hormone that acts on

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

the thyroid gland to stimulate iodide uptake to increase thyroid hormone production (Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016). For populations with developing brains (*e.g.,* fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range,[2] have been linked to decrements in neurocognitive function in offspring (Alexander et al., 2017; Thompson et al., 2018; Wang et al., 2016). There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate's mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in sensitive populations. Therefore, based on the known mode of action of perchlorate the Agency estimated potential health risks using a novel approach suggested by the EPA's Science Advisory Board (SAB for the U.S. EPA, 2013). The EPA's approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determinations

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of T3 and T4, and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (*e.g.,* the fetuses of pregnant women who might have hypothyroidism or iodide deficiency). Based on these findings, the NRC recommended a reference dose of 0.7 µg/kg/day.

Based on NRC's analysis, the EPA established a perchlorate reference dose (RfD) of 0.7 µg/kg/day in 2005 (USEPA, 2005). This value was based on a no observed effect level (NOEL) of 7 µg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

As discussed above, in 2008, the EPA derived an HRL of 15 µg/L using the RfD of 0.7 µg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (*i.e.,* food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the subpopulation identified by the NAS as likely the most sensitive to the effects of perchlorate exposure, fetuses.

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the EPA developed alternative HRLs for other sensitive populations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information (*i.e.,* drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 µg/L to 47 µg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- Derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition—to thyroid hormone changes—and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to . . . provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically free T4 (fT4)) that are associated with maternal hypothyroxinemia and subsequent

[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs . . . ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Reviews

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, *i.e.,* breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). In addition to estimating effects on breast fed infants, several reviewers recommended that the EPA shift the primary focus of its analysis to modeling the exposure implications to the fetus during early pregnancy. This was based on the knowledge that fetuses lack a functioning thyroid gland until approximately 16 gestational weeks and the substantial epidemiological evidence linking early pregnancy low fT4 levels with adverse neurodevelopmental outcomes (Endendijk et al., 2017, Korevaar et al., 2016; Morreale de Escobar, Obregón, & Escobar del Rey, 2004, Pop et al., 1999; Pop et al., 2003). Specifically, the SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: ''the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women'' (SAB for the U.S. EPA, 2013, p. 19).

The EPA considered all recommendations from the 2017 peer review. The previously developed BBDR model describing perchlorate's effects in the third trimester (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b) was calibrated only for that phase of pregnancy, not for the first trimester, and lacked a description of TSH signaling (feedback) that becomes significant as individuals become hypothyroxinemic or hypothyroid. In particular, this signaling was considered necessary to accurately predict responses of women with very low iodine intake, which was also part of the 2017 peer review recommendations. Therefore, the Lumen et al., (2009b) model needed to be revised to address these recommendations and the EPA implemented those changes needed to increase the scientific rigor of the model and modeling results. These modifications include:

- Extending the model to early pregnancy;
- Incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- Calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- Conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in January 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches in the draft *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (MCLG Approaches Report) to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018). The 2018 peer review identified a variety of strengths and limitations of the modeling (to be discussed in more detail later in this notice). The peer review panel was largely supportive of the efforts described in the MCLG Approaches Report, as evidenced by the following from the peer review final report:

Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).

The EPA also presented an alternative, population-based approach evaluating the shift in the proportion of the population that would fall below a hypothyroxinemic cut point, given exposure to perchlorate (Section 7 of the MCLG Approaches Report). This approach does not directly connect the BBDR output to a neurodevelopmental endpoint. However, for pregnant women in early pregnancy, this shift could be related to avoiding an increase in the population of offspring's risk of adverse neurodevelopmental impacts. The 2018 peer review identified strengths associated with this approach, including

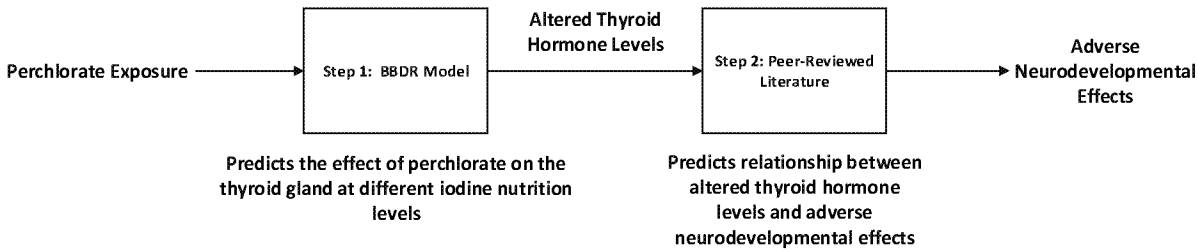
(1) the central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; (2) this approach encompasses a variety of adverse neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and (3) this approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an adverse neurodevelopmental effect. (*External Peer Reviewers for U.S. EPA, 2018, p. 7)*

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for an MCLG based on this approach to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The peer-review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. The EPA is requesting public comment in Section XIV on the adequacies and uncertainties of the methodology to derive the MCLG including the decision not to pursue this population-based approach for setting the MCLG.

Based on the comments of the peer reviewers, the EPA's final analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step

approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking water (see Figure 1). In summary, because of the known mode of action, the lack of epidemiological studies particularly in the sensitive populations and the direction of the SAB to use a "data-driven approach [which] represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages" (p. 2, SAB 2013 for U.S. EPA), the EPA uses a combination of the BBDR model that simulates perchlorate potential impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail, highlighting each step in which decisions and assumptions were made.



Note: Process figure does not imply the strength of scientific evidence.

E. Sensitive Population for Deriving MCLG

SDWA 1412(b)(4)(A) requires MCLGs to be set at a concentration in water "at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." SDWA 1412(b)(3)(C)(V) further requires that the EPA "consider the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." The EPA has interpreted these requirements to establish MCLGs that avoid adverse effects within the portions of the population that are at greater risk of adverse effects from exposure to the contaminant. The EPA is proposing an MCLG that is developed to protect the fetuses of a first trimester pregnant mother with low-iodine intake levels (*i.e.*, 75 µg/kg/day), low fT4 levels (*i.e.*, 10th percentile of an fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (*i.e.*, TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The choice of this population is consistent with discussion by the NRC (2005), and the SAB (2013). The EPA believes that by protecting this population, the other sensitive populations (*i.e.*, breast- and bottle-fed infants) will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" (USEPA, 2017; p. 73). As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake [3] (50 to 100 µg/day). Assuming 2 or 4 µg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 µg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than 75 µg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there are reports in the scientific literature suggesting that minor perturbations in thyroid hormone levels in the first trimester mother may adversely impact her offspring's neurodevelopment. Specifically, some studies show that children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) have a higher risk of reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Man, Brown, & Serunian, 1991; Pop et al., 2003; Pop et al., 1999). Notably these effects are correlated with both degree (Henrichs et al., 2010; Pop et al., 1999) and duration (Pop et al., 2003) of maternal hypothyroxinemia (SAB for the U.S. EPA, 2013, p. 10).

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. This finding is consistent with conclusions by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate (California Environmental Protection Agency, 2011, p. 90).

Specifically, two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. Costeira et al. (2011) found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in

[3] Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, Henrichs et al. (2010) found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: Preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB for the U.S. EPA, 2013). Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (*e.g.*, THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive lifestage and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- A pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and
- A pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (*e.g.*, organ volumes, blood flows) and chemical-specific information (*e.g.*, partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (*i.e.*, thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to many other PBPK models. Because perchlorate does not undergo metabolism in vivo (Clewell et al., 2007), potential uncertainty from this factor of the model is avoided since it does not need to be described.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model estimates serum thyroid hormone levels in the mother at specific gestational weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, to be health protective the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG, thereby protecting both this target sensitive population with an adequate margin of safety and those who are less sensitive with an even larger margin of safety.

The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al., (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited (Blount et al., 2006, Steinmaus et al., 2007; Leung, Pearce, & Braverman, 2010). The EPA selected an iodine intake level of 75 µg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 µg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate [4] (TSH ranges between 4.51 and 5.41 milli-international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a better approximation of the sensitive population—the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones (Blount et al., 2006; Steinmaus et al., 2013, 2016). The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: The number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH

[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism (Alexander et al., 2017). Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" (Alexander et al., 2017, p. 332). ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. (2008) is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in Table III–1.

TABLE III–1—SUMMARY OF BBDR MODEL RESULTS FOR fT4 LEVELS: PREGNANT WOMEN AT GESTATIONAL WEEK 13, ASSUMING LOW (75 μg/day) IODINE INTAKE AND WITH MUTED TSH FEEDBACK STRENGTH [A]

Perchlorate dose (μg/kg/day)	Percentile fT4 (pmol/L) [b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (−1.26%)	6.02 (−1.15%)	6.63 (−1.04%)	8.77 (−0.79%)
2	5.43 (−2.45%)	5.96 (−2.24%)	6.56 (−2.04%)	8.71 (−1.54%)
3	5.37 (−3.59%)	5.96 (−3.28%)	6.50 (−2.98%)	8.64 (−2.26%)
4	5.31 (−4.68%)	5.83 (−4.28%)	6.44 (−3.89%)	8.58 (−2.95%)
5	5.25 (−5.73%)	5.77 (−5.23%)	6.38 (−4.76%)	8.52 (−3.60%)
6	5.19 (−6.73%)	5.72 (−6.14%)	6.33 (−5.59%)	8.47 (−4.23%)
7	5.14 (−7.69%)	5.66 (−7.02%)	6.27 (−6.39%)	8.41 (−4.84%)

[a] pTSH = 0.398; see USEPA, (2018b) for additional information on pTSH.

[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67. All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestation week and did not account for variation in perchlorate and iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (*e.g.,* Blount et al., 2007) and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3). The EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4 for the identified sensitive population, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4 concentrations for women with low fT4 of childbearing age would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. To protect the most sensitive population from adverse effects, the EPA chose to use the 10th percentile from this distribution of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population.[5]

G. Epidemiological Literature

The SAB recommended that the EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Roman et al., 2013; van Mil et al., 2012). These individual studies showing that maternal hypothyroxinemia is associated with offspring neurodevelopment are also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic (Fan & Wu, 2016; Thompson et al., 2018; Wang et al., 2016). Additionally, the American Thyroid Association concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

The EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes given: (1) The body of scientific literature regarding this association, and (2) the SAB recommendation that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25). Instead, the EPA conducted a "methodologic approach to reviewing the literature" to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. More specifically, the EPA only used studies that had sufficient data to show a quantitative relationship between maternal fT4 and a neurodevelopmental outcome. The EPA acknowledges that by not giving any weight to the studies that did not show

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

a quantitative relationship between fT4 and neurodevelopmental outcomes, the Agency may be overestimating the dose of perchlorate that may be associated with adverse neurodevelopmental outcomes. This is a health protective decision that adds to the margin of safety.

Ultimately, the EPA developed a dose-response function that estimates incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

The specifics of this "methodologic approach to reviewing the literature" follow. First, the EPA identified and screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- Compatible with the sensitive life stages identified by the NRC and SAB;
- Continuous measure of thyroid hormone values (versus categorical values);
- Low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- Access to underlying data.

Second, using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible [6] with extending the BBDR model (40 studies). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia. Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior and other outcomes. The EPA notes that by selecting the papers that potentially had dose response data the Agency is deviating from the systematic weight of evidence review approach to identify those studies that the SAB recommended we examine to derive the MCLG.

Third, from these 15 papers five were selected for dose response assessment—four related to cognition (Finken et al., 2013; Korevaar et al., 2016; Pop et al., 2003, 1999) and one related to behavior (Endendijk, Wijnen, Pop, & van Baar, 2017). The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-response assessment (*e.g.,* dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al., (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

As laid out for the peer reviewers, for each study that met the criteria identified above for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018b). These relationships were either presented in the original published paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to assure consideration of the populations likely to be at greater risk from the dose of perchlorate associated with a given change in fT4.

Table III–2 provides a summary of the changes in fT4 predicted to produce a 1, 2, and 3 percent decrease in any given neurodevelopmental effect and corresponding perchlorate doses. The choice of 1, 2, and 3% is based on the analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI). Specifically, a 1%, 2%, or 3% change from the standardized mean for each test (*i.e.,* 100 points) equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively (Endendijk et al., 2017; Finken et al., 2013).

These results provide the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (derived from the epidemiologic literature [7]).

[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (*i.e.,* at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (*i.e.,* hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (*i.e.,* when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the MCLG Approaches Report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

Table III-2. Estimated Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopment for the Population of Low-Iodine Intake Women of Reproductive Age Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	End-point	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al., (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1
Korevaar et al., (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8
Pop et al., (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al., (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al., (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6

Study	End-point	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
Endendijk et al., (2017)	Anxiety/ depress-sion score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al., (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

H. Identifying a Point of Departure for Developing the MCLG

From the seven analyses presented in Table III–2 above, the EPA chose to use its independent analysis of the Korevaar et al., (2016) data (comprising of 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. There are three reasons for this selection: (1) There is sufficient quantitative data to derive a health impact function for the sensitive population of interest; (2) the analysis adjusts for an appropriate set of confounders, and (3) the neurodevelopmental endpoint—intelligence quotient (IQ)—is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below). The other studies presented in Table III–2 do not provide one or more of these features (USEPA, 2018b).

The five identified papers evaluated a variety of endpoints with Korevaar et al., (2016) evaluating IQ, Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) using the Bayley Scale to evaluate PDI and MDI, Finken, van Eijsden, Loomans, Vrijkotte, and Rotteveel (2013) evaluating the SD of reaction time, and Endendijk, Wijnen, Pop, and van Baar (2017) evaluating anxiety/depression scores using the Child Behavioral Check List (CBCL). The SD of reaction time from Finken et al., (2013) was not well-received by the peer reviewers (External Peer Review for U.S. EPA, 2018) because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al., (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al., (2017) nor the Finken et al., (2013) analyses had functions for the sensitive life stage (*i.e.*, their analyses were based on the full range of fT4 levels and did not concentrate on the impacts of low-end fT4 levels). For these reasons, the Endendijk et al., (2017) and Finken et al., (2013) papers were not selected for further evaluation.

The Korevaar et al., (2016) original and independent analyses are preferable compared to the Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) studies because neither function derived from the Pop et al., studies was adjusted for confounders. Additionally, both Pop et al., papers have an N <50 compared to the Korevaar et al., analyses, which have an N of greater than 3,600.[8]

Although the original Korevaar et al., (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al., (2016) EPA reanalysis was chosen over the original analysis because it included modifications to the analysis at the suggestion of the peer review panel. The

[8] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609 due to the exclusion of subjects with imputed values for maternal fT4.

revised analysis controls for a more parsimonious set of confounders (*e.g.*, previously included variables such as infant gender, maternal parity, birthweight, mother's body mass index (BMI), and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al., (2016) model because of the feedback received during the peer review of the MCLG Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

Korevaar et al., [2016] controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al., (2016) data, and making decisions about data quality and influential data points in the analysis. That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values. Subsequently, the EPA selected the Korevaar et al., (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ.[9]

As indicated above, the EPA has utilized a health protective approach to this analysis consistent with the SDWA definition of the MCLG. The peer reviewers commented that this approach was fit-for-purpose. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. As explained earlier, the results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior, and other outcomes such as autism. Among these studies, only 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al., (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al., (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek et al., 2017; Roman et al., 2013; Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al., (2011) and Gyllenberg et al., (2016). Although Endendijk et al., (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al., (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al., (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al., (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (*i.e.*, not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking.

Not every paper the EPA located in its literature review found a statistically

[9] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the MCLG Approaches Report.

significant association between maternal fT4 as a continuous variable (*i.e.,* the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses (Fan & Wu, 2016; Thompson et al., 2018 and Wang et al., 2016), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. Therefore, the EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data. In an attempt to minimize uncertainty, the EPA reanalyzed the data collected by Korevaar et al., (2016) using a spline function that estimates a coefficient specifically for the low range of the fT4 data.

There are a variety of neurodevelopmental endpoints used to examine behavior and cognition in children (*e.g.,* intelligence quotient (IQ), motor skills, vocabulary and language development, stimulus responsiveness, etc.). The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al., (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. As such, in the derivation of the MCLG, IQ is a surrogate for a suite of potential neurodevelopmental effects that might occur to the offspring of hypothyroxinemic and iodine deficient mothers.

There are several different tests that are widely used to measure IQ in children, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

Associations have been found between IQ scores and both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al., (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). Research suggests that children's rearing environment, including parental education, while growing up may increase IQ scores in adolescence by several points (*e.g.,* Kendler et al., 2015).

IQ scores have been used to help diagnose disorders such as intellectual disability and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM–V) IQ scores are used in an individual's comprehensive assessment to determine intellectual disability, which pairs standardized testing of intelligence with a clinical assessment of adaptive functioning. Intellectual disability is considered for individuals with an IQ score of about 70 or below (American Psychiatric Association, 2013).

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 percent extra risk (for discrete data), or a 1 standard deviation (*i.e.,* 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint. Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, USEPA, 2012).

For the specific context of setting an MCLG for perchlorate, the EPA made a policy decision to evaluate the level of perchlorate in water associated with a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in the mean population IQ (*i.e.,* 1, 2 and 3 IQ points). The EPA selected IQ as a surrogate for neurodevelopmental effects based upon its evaluation of the epidemiologic literature describe above. The need to utilize the best available peer reviewed data to inform scientific assumptions and policy choices to meet the statutory requirements associated with developing an MCLG under the SDWA highlights the challenges associated with regulating chemicals for which potential effects are indirect, and scientific data do not address all uncertainties. The Agency must make a policy decision informed by science, consistent with statutory requirements even in situations where the data do not provide clear choices. To develop the proposed MCLG for perchlorate, the EPA made a policy decision to use a 2 IQ point decrement in the population-distribution of IQ for the sensitive population. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants for which there is concern about potential thyroid effects, either under the SDWA or other statutory frameworks.

Applying these response rates to the results from the reanalysis of Korevaar et al., (2016), results in a POD dose of 3.1 μg/kg/day for a 1 point decrease in the sensitive population's IQ, a POD dose of 6.7 μg/kg/day for a 2 point decrease in the sensitive population's IQ, and a POD dose of 10.8 μg/kg/day for a 3 point decrease in the sensitive population's IQ. These PODs associated with a 1, 2, or 3 point decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the POD is designed to provide an adequate margin of safety for the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 μg/day and a TSH feedback loop that is less than 60% as effective as individuals with median

TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the methodological reasons described previously, the EPA believes that the selection of these parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive population and allows for an adequate margin of safety.

I. Translate PODs to RfDs

When deriving an RfD the EPA evaluates whether to apply uncertainty/variability factors to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002). As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: Inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a no-observed-adverse-effect-level (NOAEL), and an incomplete database. The factors are intended to account for: (1) Variation in susceptibility among the members of the human population (*i.e.,* inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (*i.e.,* interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (*i.e.,* extrapolating from subchronic to chronic exposure); (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) uncertainty associated with extrapolation when the database is incomplete. (U.S. EPA, 2011b) The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (*i.e.,* uncertainty factor (UF) for within-human variability/inter-individual variability, UF_H). For this analysis a UF of 3 is used. The approach taken to derive the RfD attempts to address variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes.[10] There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (*i.e.,* no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.

Further, as discussed in section III.C. of this preamble the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. In addition, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is potentially because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et al., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the fetal thyroid begins secreting thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels available to the fetus. Given that the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. Therefore, as described above, the EPA selected an intraspecies UF of 3 to account for the uncertainties in modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children.

The EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship.[11] As noted above, the Agency has opted to apply a UF of 3 to the POD, which adds an adequate margin of safety to the MCLG derivation. Section 4.4.5.3 (p. 4–42) of *A Review of the RfD & RfC Processes* recommends reducing the intraspecies UF from a default of 10 "only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)" (p. xviii, USEPA, 2002). The EPA selected a UF of 3 instead of the full 10 because the modeled groups within the population that are identified as likely to be at greater risk to perchlorate in drinking water (*i.e.,* the fetus of the iodide deficient pregnant mother) and has selected model parameters to account for the most sensitive individuals in that group (*i.e.,* muted TSH feedback, low fT4 values, low-iodine intake).

Below we list the other uncertainty factors added and the justification.

- Uncertainty in extrapolating animal data to humans (*i.e.,* interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this factor is not applicable since animal studies were

[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the MCLG Approaches Report.

[11] As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (*i.e.,* lack of knowledge) . . . whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.

• Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (*i.e.*, extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.

• Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.

• Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).

• The product of all the uncertainty factors (UF_H) is 3 ($3 \times 1 \times 1 \times 1 \times 1$).

Below we generate RfD's for each of the points of departure.

Using the POD of 6.7 μg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.2\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 μg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.0\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 μg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

J. Translate RfD Into an MCLG

To translate the RfD (μg/kg/day) to a concentration in drinking water (μg/L), the EPA used the following equation:

$$W\ \left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

Where:

W = drinking water concentration of perchlorate in micrograms per liter (μg/L);

RfD = reference dose (1.03 μg/kg/day for a 1 percent decrease in IQ, 2.23 μg/kg/day for a 2 percent decrease in IQ, or 3.6 μg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution of drinking water to overall perchlorate exposure.

To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate specific to women of childbearing age (*i.e.*, non-pregnant, non-lactating, 15–44 years of age (0.032 L/kg/day). This decision is consistent with the analysis used in deriving an RSC, which was performed using food consumption information for a population of women of childbearing age from NHANES. The 90th percentile is chosen to account for variability in drinking water ingestion rates, but also adds another layer of health protection for 90% of women (Table III–3).

The EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable. The use of the drinking water intake for 15–44 year old women is consistent with the analysis used in deriving an RSC_w (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20–44 years of age). The age range used to develop the

RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the EPA's Exposure Factors Handbook (USEPA, 2011c) identifies drinking water ingestion rates for women 15–44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis.

TABLE III–3—CONSUMERS-ONLY ESTIMATED DIRECT AND INDIRECT COMMUNITY WATER INGESTION RATES FROM KAHN AND STRALKA (2008)

[L/kg/day]

Female population categories	Sample size	Mean	90th Percentile	95th Percentile
Pregnant	65	[a] 0.014	[a] 0.033	[a] 0.043
Lactating	33	[a] 0.026	[a] 0.054	[a] 0.055
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States,* 1994–1996 (FASEB/LSRO, 1995).

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2019c). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in about 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20–44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (µg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The details of these assumptions are explained on page 5–5 of the Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (USEPA 2019c). Specifically, the EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the 20 samples included in the TDS data. In order to estimate the 95th percentile from the 20 samples, the EPA used the second-highest test result for each food to represent the 95th percentile concentration. While simple, this method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine (Carriquiry et al., 2016). The aforementioned method for identifying the 95th percentile concentration of perchlorate from food was selected over other, more "statistically based" methods for estimating percentiles as it avoids the need to assume a distributional shape for the samples. The EPA determined that it was more reliable to assume the empirically derived distribution as the basis for selecting the 95th percentile (*i.e.,* assuming the distribution was equal to the distribution of samples collected in the TDS), as opposed to forcing a distributional shape, such as normal or log-normal, onto the data that may not necessarily be appropriate. With the chosen method, we can at least be sure that the distributional shape is appropriate for the data at hand, whereas by choosing the alternative that assumes a distributional shape, in many instances we would not even be certain of that. The EPA used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20–44.

Table III–4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20–44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 µg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile perchlorate food concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

TABLE III–4—PERCHLORATE DOSE FROM FOOD (µg/kg/day) IN U.S. WOMEN AGES 20–44 USING THE MEAN AND 95TH PERCENTILE TDS RESULTS [1]

Level of bodyweight adjusted perchlorate consumption from population distribution	Perchlorate dose from food (µg/kg/day)	
	Based on mean concentrations of perchlorate in food	Based on 95th percentile concentrations of perchlorate in food
Mean	0.09–0.12	0.23–0.24
50th Percentile	0.08–0.10	0.17–0.19
90th Percentile	0.18–0.21	**0.45**
99th Percentile	0.33–0.38	1.16–1.17

[1] Ranges are due to various approaches for handling values level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value.

The EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III–5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using the EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.0	56%	0.032	18
2.2	80%	0.032	56
3.6	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss, 2-point IQ loss, or a 3-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the NPDWR. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 µg/L based on the rationale and methology described in Section III above. The derivation of the proposed MCLG uses a point of departure based upon a two percent decrease in IQ for offspring of hypothyroxinemic women of child bearing age have with low iodine intake. The EPA selected a 2 percent decrease in IQ for the proposed

perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the subpopulation of interest.

As described in Section III, the EPA has selected model parameters and other factors for the derivation of the MCLG that are health protective, including the focus on the most sensitive life stage. The EPA believes that the selection of the combination of protective parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive subpopulation and allows for an adequate margin of safety. The EPA also acknowledges the uncertainties in the derivation of the proposed (and alternative) MCLGs. The EPA acknowledges in particular the challenge associated with selecting the decrement of IQ that represents an adverse effect at the population level and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement given the absence of robust human epidemiological data directly linking perchlorate exposure to IQ decrements. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2019b). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018c). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

Because the EPA is taking comment on alternative MCLG values of 18 µg/L and 90 µg/L the Agency evaluated the feasibility of setting an MCL at these levels. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this level under field conditions (USEPA 2018a, 2019b). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)), including: The quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII in this preamble. The EPA must base its action on the best available, peer-reviewed science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA Section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The UCMR 1 is the primary source of occurrence data the EPA relied on to estimate the number of water systems (and associated population) expected to be exposed at levels of perchlorate which could potentially exceed the proposed and alternative MCL levels. Since UCMR 1 data was first used to inform the Agency actions on the 2008 preliminary regulatory determination and the 2011 final regulatory determination, the Agency has modified its analysis of the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions at some States that have enacted perchlorate regulations since the UCMR 1 data was collected. Despite these updates, the EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants (USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- All 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to the EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 µg/L for perchlorate in the UCMR.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

In September of 2012, the EPA received a "Request for Correction"

letter from the United States Chamber of Commerce regarding information and data (*i.e.*, the occurrence of perchlorate in drinking water) used by the EPA in its 2011 determination to regulate perchlorate. The U.S. Chamber of Commerce letter stated that the EPA relied upon: (1) Data that did not comply with data quality guidelines and (2) data that was not representative of current conditions.

In response [12] to the U.S. Chamber of Commerce, the EPA conducted a detailed assessment of the source water sample detections and determined that it was most appropriate to exclude the source water sample detections from the UCMR 1 perchlorate data set when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 perchlorate data set. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 perchlorate data set. As a result of the assessment, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the entry point to the distribution system. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections from 149 PWSs.

Table VI–1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

In response to the U.S. Chamber of Commerce request, the EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two states. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 (MassDEP, 2006), and California promulgated a drinking water standard of 6 μg/L in 2007 (California Department of Public Health, 2007). Systems in these states are now required to keep perchlorate levels in drinking water below their state limits, which are lower than the proposed MCL and alternative MCLs. Therefore, the UCMR 1 sampling results from systems in these states do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. The notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

To update the occurrence data for systems sampled during UCMR 1 from the States of California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (*https://sdwis.waterboards.ca.gov/PDWW/*) and Massachusetts (*https://www.mass.gov/service-details/public-water-supplier-document-search*) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

Out of the 540 detections previously described the EPA updated data for 321 detections (320 from California systems and 1 from a Massachusetts system). The convention used by the EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported compliance monitoring data, if more than one data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were the EPA could not find updated entry point data, then the original data from UCMR 1 for such entry point was kept.

TABLE VI–1—UCMR 1 DATA SUMMARY STATISTICS

Item	Small system sample	Large system census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥4 μg/L	15	525	540
Sample measurements >18 μg/L	1	16	17
Sample measurements >56 μg/L	0	2	2
Sample measurements >90 μg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥4 μg/L	8	328	336
Entry points at which measurements >18 μg/L	1	16	17
Entry points at which measurements >56 μg/L	0	2	2
Entry points at which measurements >90 μg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥4 μg/L	8	141	149
Systems at which measurements >18 μg/L	1	14	15
Systems at which measurements >56 μg/L	0	2	2
Systems at which measurements >90 μg/L	0	1	1

Source: (USEPA, 2019b). The total row counts and counts of measurements ≥4 μg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 μg/L. The instances where perchlorate measurements equal or exceed either 18 μg/L, 56 μg/L, or 90 μg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 μg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

[12] See the EPA response letter at *https://www.epa.gov/sites/production/files/2017-08/documents/12004-response_0.pdf.*

Table VI–2 shows the service populations that correspond with the occurrence summary in Table VI–1. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points; *e.g.,* the entry point population for a system with two entry points is one-half the total system population.

TABLE VI–2—UCMR1 DATA SERVICE POPULATION SUMMARY STATISTICS

Item	Small system sample	Large system census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥4 μg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements >18 μg/L	2,155	618,406	620,560
Population served by entry points at which measurements >56 μg/L	0	32,432	32,432
Population served by entry points at which measurements >90 μg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥4 μg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 μg/L	4,309	696,871	701,180
Population served by systems at which measurements >56 μg/L	0	64,733	64,733
Population served by systems at which measurements >90 μg/L	0	25,972	25,972

Source: (USEPA, 2019b). The populations for entry points/systems with measurements ≥4 μg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 μg/L. The instances where perchlorate measurements equal or exceed either 18 μg/L, 56 μg/L, or 90 μg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 μg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCLs. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI–3 through Table VI–5 show the occurrence and exposure estimates based on the 56 μg/L, 18 μg/L MCL, and 90 μg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

TABLE VI–3—ESTIMATED PERCHLORATE OCCURRENCE AND EXPOSURE: ENTRY POINT MAX EXCEEDS 56 μG/L

Affected entity	Small systems	Large systems	Total systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: (USEPA, 2019b).

TABLE VI–4—ESTIMATED PERCHLORATE OCCURRENCE AND EXPOSURE: ENTRY POINT MAX EXCEEDS 18 μg/L

Affected entity	Small systems [1]	Large systems	Total systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: (USEPA, 2019b).

[1] The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 μg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% × 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 μg/L.

TABLE VI–5—ESTIMATED PERCHLORATE OCCURRENCE AND EXPOSURE: ENTRY POINT MAX EXCEEDS 90 μg/L

Affected entity	Small systems [1]	Large systems	Total systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: (USEPA, 2019b).

In summary, the perchlorate occurrence information suggests that at an MCL of 56 μg/L, two systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. One of these two systems would exceed the alternative MCL of 90 μg/L. In addition, at an MCL of 18 μg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is "feasible", the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, the SDWA directs the EPA to determine that it is economically and technologically feasible to ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain "criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels." (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report (USEPA, 2019b).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: Detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of sample analysis and data reporting. All of the proposed EPA analytical methods provide performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

EPA Method 314.0, "Determination of Perchlorate in Drinking Water Using Ion Chromatography" (Revision 1.0, USEPA, 1999a) has a method detection limit (MDL) of 0.53 μg/L. Single-laboratory mean percent recovery in various aqueous matrices range from 86% to 113% with Relative Standard Deviations (RSDs) of 1.0% to 12.8%. A minimum reporting level (MRL) is not specified in the method; however, a range of 3.0 to 5.0 μg/L is cited as a benchmark range for quality assurance/quality control (QA/QC) procedures. The MRL is to be established as either a concentration that is greater than three times the laboratory MDL or at a concentration that yields a response greater than a signal to noise ratio of five. In either case, the MRL must not be below the lowest instrument calibration standard (USEPA, 1999a). Method 314.0 was widely adopted as the standard perchlorate method.

After the EPA published Method 314.0, the Agency adopted additional method development goals for the analysis of perchlorate in drinking water including: (1) Reducing MRL to less than 1 μg/L through the application of sample concentration techniques, microbore analytical columns, and advanced detection systems (*i.e.,* mass spectrometry), (2) further increasing the tolerance for high ionic strength matrices, and (3) enhancing measurement selectivity.

EPA Method 314.1, "Determination of Perchlorate in Drinking Water Using Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection" (Revision 1.0, USEPA, 2005b) documents the EPA single-laboratory Lowest Concentration Minimum Reporting Levels (LCMRLs) of less than 0.2 μg/L (DL = 0.03 μg/L) using online sample pre-concentration. The method uses matrix diversion to handle high ionic strength matrices (up to 1,000 mg/L TDS) and added confirmation analysis using a second analytical column (USEPA, 2005b).

EPA Method 314.2, "Determination of Perchlorate in Drinking Water Using Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection" (USEPA, 2008c) documents the EPA single-laboratory LCMRLs of less than 0.1 μg/L (DLs <0.02 μg/L) using large volume injection. The method uses 2–D chromatography to handle high ionic strength matrices (up to 1,000 mg/L total dissolved solids [TDS]) and eliminates the need for separate confirmation analysis (USEPA, 2008c).

EPA Method 331.0, "Determination of Perchlorate in Drinking Water by Liquid Chromatography Electrospray Ionization Mass Spectrometry" (Revision 1.0, USEPA, 2005c) documents the EPA single-laboratory LCMRLs of less than 0.1 μg/L (DLs <0.01 μg/L), applied multiple analytical advancements to a liquid chromatography (LC) analysis including a perchlorate selective LC column (AS–21), mass spectrometry (MS) or MS/MS detection for selectivity and sensitivity, and a custom labeled internal standard ($Cl^{18}O_4^-$) (USEPA, 2005c).

EPA Method 332.0, "Determination of Perchlorate in Drinking Water by Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry" (USEPA, Revision 1.0, 2005d) documents the EPA single-laboratory LCMRL of 0.1 μg/L (DL = 0.02 μg/L), applied multiple analytical advancements in an IC analysis including suppressed conductivity IC, MS or MS/MS selectivity and sensitivity, and a custom labeled internal standard ($Cl^{18}O_4$) (USEPA, 2005d).

VIII. Monitoring and Compliance Requirements

A. What are the proposed monitoring requirements?

The EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework set out in 40 CFR 141 Subpart C (Standardized Monitoring Framework). Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. The EPA is proposing that consistent with the standardized monitoring framework water systems would be initially required to monitor quarterly for perchlorate. The EPA is also proposing that based upon the monitoring results States would be able to reduce the monitoring frequency to annually, once every three years or once every nine years if the State concludes that the system is reliably and consistently below the MCL. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point in the next quarter after the violation occurred (40 CFR 141.23(c)(7)). The state may allow the system to return to the reduced monitoring frequency when the state determines that the system is reliably and consistently below the MCL. However, the state cannot make a determination that the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples below the MCL have been collected (40 CFR 141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the state (40 CFR 141.23(c)(6)).

B. Can states grant monitoring waivers?

Under this proposal, water systems may apply to the state, and states may grant, a 9-year monitoring waiver for perchlorate if the conditions described in 40 CFR 141.23(c)(3)–(6) are met. A state may grant a waiver for surface water systems after three rounds of annual monitoring with results less than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are system MCL violations determined?

Under this proposal, violations of the perchlorate MCL would be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the perchlorate MCL would be determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When must systems complete initial monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than 10,000 persons must collect 4 quarterly samples for perchlorate during the second compliance period of the fourth compliance cycle (January 1, 2023–December 31, 2025) of the Standardized Monitoring Framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the third compliance period of the fourth compliance cycle (January 1, 2026–December 31, 2028) of the Standardized Monitoring Framework.

E. Can systems use grandfathered data to satisfy the initial monitoring requirements?

As proposed today, systems would be allowed to use grandfathered perchlorate data collected after January 1, 2020, to satisfy the initial monitoring requirements. To satisfy initial perchlorate monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for CWSs serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for NTNCWs and for CWSs serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report requirements?

A community water system must prepare and deliver to its customers an annual Consumer Confidence Report (CCR) in accordance with requirements in 40 CFR 141 Subpart O. A CCR provides customers with information about their local drinking water quality as well as information regarding the water system compliance with drinking water regulations. Under this proposal CWSs would be required to report perchlorate information in their CCR.

B. What are the public notification requirements?

All public water systems must give the public notice for all violations of NPDWRs and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, per 40 CFR 141.202(b)(1), notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation under this proposal.

X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by states to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in states issuing small system variances under Section 1412(e) of the SDWA.

The Agency solicits public comment on the choice of available treatment technologies discussed in this section.

A. What are the best available technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) The capability of a high removal efficiency;

(2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

- Ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (*e.g.*, a new well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water (Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008). The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, *i.e.*, the contaminant "breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough—called bed volumes—the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes (Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010).

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed (*i.e.*, operated on a 'throw-away' basis). This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste (Blute *et al.*, 2006; Russell *et al.*, 2008; Wu & Blute, 2010). Ion exchange can increase the corrosivity of treated water (Berlien, 2003; Betts, 1998; USEPA, 2005b) because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench-scale tests and full-scale treatment plant studies (Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T.D. Webster & Crowley, 2010, 2016; T.D. Webster & Litchfield, 2017). Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 (T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017). Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible (Dugan, 2010b, 2010a; Dugan *et al.*, 2009). This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus (Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009).

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, *e.g.*, through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer (U.S. Department of Defense (U.S. DoD), 2008, 2009) or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides (Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017). The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya *et al.*, 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as

concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent (Liang, Scott, Palencia, & Bruno, 1998; Nam *et al.*, 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005). While water quality affects process design (*e.g.*, recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (*e.g.*, 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water. Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the small system compliance technologies?

The EPA is proposing the SSCT shown in Table X–1. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability (USEPA, 2018a).

TABLE X–1—PROPOSED SSCT FOR PERCHLORATE REMOVAL

System size (population served)	Ion exchange	Biological treatment	Reverse osmosis	Point-of-use reverse osmosis
25–500	Yes	No	No	Yes.
501–3,300	Yes	Yes	Yes	Yes.
3,301–10,000	Yes	Yes	Yes	Not applicable.[a]

[a] For perchlorate, the EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

The SSCT listed in Table X–1 include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Organizations (*e.g.*, NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: Steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules (USEPA, 1998). The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of median household income. Table X–2 shows the expenditure margins derived for the analysis. These margins show the cap on affordable incremental annual expenditures.

TABLE X–2—EXPENDITURE MARGINS FOR SSCT AFFORDABILITY ANALYSIS

System size (population served)	Median household income[a] (a)	Affordability threshold[b] (b) = 2.5% × a	Baseline water cost[c] (c)	Expenditure margin (d) = b − c
25–500	$52,791	$1,320	$341	$979
501–3,300	51,093	1,277	395	883
3,301–10,000	55,975	1,399	412	987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a).
[a] MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates (U.S. Census Bureau, 2010) stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons (Bureau of Labor Statistics (BLS), 2018b).
[b] Affordability threshold equals 2.5 percent of MHI.
[c] Household water costs derived from 2006 Community Water System Survey (USEPA, 2009c), based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

Table X–3 shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small*

System Compliance Technologies for Perchlorate in Drinking Water (USEPA, 2018a) and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c). Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

TABLE X–3—ANNUAL INCREMENTAL COST ESTIMATES FOR SSCT AFFORDABILITY ANALYSIS

System size (population served)	Ion exchange	Biological treatment	Reverse osmosis	Point-of-use reverse osmosis
25–500	$378 to $610	$2,146 to $3,709	$2,272 to $2,671	$265 to $271.
501–3,300	$98 to $148	$324 to $566	$561 to $688	$250 to $251.
3,301–10,000	$104 to $153	$211 to $315	$431 to $493	Not applicable.[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a), which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.

[a] For perchlorate, the EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the requirements for primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA Sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State recordkeeping requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (*i.e.*, primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State reporting requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant. However, the perchlorate MCL could result in a greater frequency of reporting by certain states. See discussion of Paperwork Reduction Act compliance in Section XVI for more information.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);
- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);
- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as

infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);

- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If the EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and—in a limited number of cases—costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B below summarizes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section C below summarizes this method used to estimate these benefits.

Section D below provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a), which is available in the docket for the proposed rule. Section XIII summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

Some costs associated with an NPDWR are incurred by all CWS and NTNCWS (*e.g.*, monitoring and reporting) while others are only incurred by systems with perchlorate levels exceeding the MCL. The EPA estimated costs for CWS and NTNCWS to monitor and report perchlorate levels and also estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment because it is the most cost-effective treatment option and easy to operate on a 'throw-away' basis. If site-specific nontreatment options are available and lower cost, then this assumption might overstate costs. The EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring, report results, and apply for waivers. For the purpose of these estimates, the EPA assumed that both small and large systems would require the same amount of time to read the rule, apply for a waiver, and collect a water sample but that it would take large systems twice as long to provide initial training to their staff. Table XII–1 summarizes the frequency and labor hour assumptions for this analysis.

TABLE XII–1—LABOR HOURS FOR DRINKING WATER SYSTEMS ADMINISTRATIVE AND MONITORING REQUIREMENTS

Activity	Frequency	Small system hours	Large system hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample [1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.

[1] The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points × 4 samples × 1 hour per sample).

Systems will incur monitoring costs over the analysis period. The EPA estimated monitoring frequency based on the proposed initial monitoring requirements, the standard monitoring framework requirements for inorganic contaminants, and the proposed implementation schedule. The estimated number of monitoring samples over the analysis period shown in Table XII–2 reflect the following phases:

1. Initial monitoring; four quarterly samples at every CWS and NTNCWS entry point.
2. Preliminary regular monitoring before waiver application: Three regular monitoring samples for every CWS and NTNCWS entry point (collected annually at surface water system entry points and triennially at ground water system entry points).
3. Long-term monitoring at either (a) regular monitoring frequency for entry points at systems not granted waivers (60% of surface water system and 10% of ground water systems), or (b) reduced monitoring frequency for entry points at systems receiving waivers from primacy agencies (40% of surface water systems and 90% of ground water systems), which is one sample during every nine-year compliance monitoring cycle.

TABLE XII–2—ESTIMATES OF COMPLIANCE MONITORING SAMPLES BY PHASE AND SYSTEM TYPE, SIZE, AND SOURCE WATER

Monitoring phase (sampling frequency)	System type, size, and source water	Number of entry points [1]	Aggregate samples [2]
1. Initial monitoring (4 quarterly samples in one year)	All CWS and NTNCWS	92,656	370,624

TABLE XII–2—ESTIMATES OF COMPLIANCE MONITORING SAMPLES BY PHASE AND SYSTEM TYPE, SIZE, AND SOURCE WATER—Continued

Monitoring phase (sampling frequency)	System type, size, and source water	Number of entry points [1]	Aggregate samples [2]
2. Preliminary regular monitoring (3 annual entry point samples for surface water systems and 3 triennial entry point samples for ground water systems).	All CWS and NTNCWS	92,654	277,962
3a. Long-term monitoring, no waiver (annual entry point samples).	60% of large surface water CWS	3,324	86,424
	60% of small surface water CWS and all surface water NTNCWS.	6,064	139,472
3a. Long-term monitoring, no waiver (triennial entry point samples).	10% of large ground water CWS	680	4,080
	10% of small ground water CWS and all ground water NTNCWS.	7,021	35,105
3b. Long-term monitoring, waiver (1 sample every 9 years).	40% of large surface water CWS	2,216	4,432
	40% of small surface water CWS and all surface water NTNCWS.	4,043	8,086
3b. Long-term monitoring, waiver (1 sample every 9 years).	90% of large ground water CWS	6,117	12,234
	90% of small ground water CWS and all ground water NTNCWS.	63,189	63,189

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA–HQ–OW–2018–0780).

[1] The EPA estimated a total of 92,656 entry points based on the total number of potentially affected systems in SDWIS/FED and the average number of entry points per system in the UCMR 1 data by size category and source water. The initial monitoring phase includes all entry points. The EPA assumed that the two entry points with MCL exceedances at the proposed MCL of 56 µg/L would continue to take quarterly samples for the duration of the analysis period, for a total of 232 samples. Thus, they are excluded from the estimates for the subsequent phases of regular and long-term monitoring. Primacy agencies may, however, allow monitoring to return to a regular schedule if treatment process operation can reliably and consistently reduce perchlorate below the MCL.

[2] For Phase 3, the estimate of aggregate samples is the product of the number of entry points and the frequency of sampling during the remaining years of the analysis period. For example, large surface water CWS without a waiver conduct long-term annual monitoring for 26 years because they complete preliminary regular monitoring in year 9. In contrast, large ground water CWS without a waiver begin long-term triennial monitoring in year 16 because their preliminary regular monitoring phase lasts for 9 years (3 triennial samples) instead of 3 years (3 annual samples). The estimates also reflect schedule differences by size because large CWS begin monitoring schedules three years earlier than small CWS and all NTNCWS.

To estimate costs to CWSs and NTNCWSs associated with time spent on compliance monitoring and other administrative costs, the EPA generally uses the labor rate [13] for full-time treatment plant operators in CWSs from USEPA (2011c), which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of system entry points that exceed the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system.[14] The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and nontreatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (*e.g.,* 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, the EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 µg/L the blending target would be 45 µg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost curves from the WBS models to the design and average flows adjusted for

[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c) contains more complete discussion of the WBS models and the cost estimating approach.

blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and Agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII–3 summarizes the labor hour assumptions for these activities. The EPA requests comments on these assumptions.

TABLE XII–3—LABOR HOURS FOR PRIMACY AGENCY ADMINISTRATIVE REQUIREMENTS

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes [1]	one time per Agency	416
Provide initial training and assistance to water systems [2]	total per Agency	2,080
Provide initial training to staff [2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a).

[1] The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.

[2] The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19–2041 (State Government—Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report (Bureau of Labor Statistics (BLS), 2016 Table 3), for a fully loaded hourly wage rate for States of $50.67. The EPA requests comments on these labor rate assumptions.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (*i.e.,* years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (*i.e.,* years 7 to 9 of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring—one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring—once every nine years—under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with USEPA (2008b), the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (*i.e.,* year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level.[15] To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size (U.S. Census Bureau, 2017b). The EPA divided the total annual system-level costs by the number of households served by the system.

C. Method for Estimating Benefits

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves (a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and (b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et

[15] For systems with monitoring costs only, household-level costs will be negligible.

al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15–44) in the US, which is 19.7 percent (U.S. Census Bureau, 2017a). The number of women of childbearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) (Martin, Hamilton, & Osterman, 2017).

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 µg/L and alternative MCLs of 18 µg/L and 90 µg/L. The first step relates changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake. For the BBDR simulations, the EPA used the 90th percentile ingestion rate to be consistent with the MCLG modeling approach, which may overstate the exposure in the simulation.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the Korevaar et al., (2016) study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII–4 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

TABLE XII–4—PROPORTION OF POPULATION BASED ON MATERNAL IODINE INTAKE STATUS

Iodine intake range (µg/day) used for benefits analysis	Proportion of the population (%)
0 to <55	7.14
55 to <60	2.15
60 to <65	1.06
65 to < 70	1.86
70 to <75	1.31
75 to <80	3.10
80 to <85	2.62
85 to <90	1.20
90 to <95	1.83
95 to <100	2.94
100 to <125	13.56
125 to <150	9.08
150 to <170	10.31
170 to <300	24.47
≥300	17.36

Source: U.S. EPA (2019a).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants that target the thyroid, such as nitrate, as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XIII provides additional discussion of uncertainties in this analysis.

D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 µg/L, Table XII–5 summarizes the total estimated cost of the proposed rule to water systems and primacy agencies, and Table XII–6 summarizes the estimated per-household cost for the system incurring treatment costs.[16] Table XII–7 summarizes the estimated benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

TABLE XII–5—SUMMARY OF TOTAL ANNUALIZED COSTS AT MCL OF 56 µg/L

[Millions; 2017$]

Cost component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	5.93	6.38
Drinking Water Systems Costs Subtotal	6.58	7.07
State Administration Costs	3.09	3.20
Total Costs	9.67	10.28

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

[1] Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (*e.g.,* well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

TABLE XII–6—SUMMARY OF HOUSEHOLD-LEVEL ANNUAL COSTS FOR SYSTEMS TREATING TO COMPLY WITH MCL AT 56 μg/L

[2017$]

Cost range	3% Discount	7% Discount
Minimum	$11	$14
Average	40	47
Maximum	69	80

Source: (USEPA, 2019a).

TABLE XII–7—SUMMARY OF TOTAL ANNUALIZED BENEFITS OF AVOIDED LOST IQ DECREMENTS AT MCL OF 56 μg/L

[Millions; 2017$]

Korevaar β distribution	Annual delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	2.00	0.34
Lower	30	0.44	0.07

Source: (USEPA, 2019a).

For the alternative MCL of 18 μg/L, Table XII–8 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII–9 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII–10 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

TABLE XII–8—SUMMARY OF TOTAL ANNUALIZED COSTS AT MCL OF 18 μg/L

[Millions; 2017$]

Cost component	3% Discount (UCMR 1) [1]	7% Discount (UCMR 1) [1]	3% Discount (national) [1]	7% Discount (national) [1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	5.94	6.38	5.94	6.38
Drinking Water Systems Costs Subtotal	12.85	13.67	13.86	14.75
State Administration Costs	3.09	3.21	3.09	3.21
Total Costs	15.95	16.88	16.95	17.96

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.

[1] The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 μg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% × 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 μg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.

[2] Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (*e.g.,* well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

TABLE XII–9—SUMMARY OF HOUSEHOLD-LEVEL ANNUAL COSTS FOR SYSTEMS TREATING TO COMPLY WITH THE MCL AT 18 μg/L

[2017$]

Cost range	3% Discount (UCMR 1) [1]	7% Discount (UCMR 1) [1]	3% Discount (national) [1]	7% Discount (national) [1]
Minimum	$18	$24	$18	$24
Average	38	46	38	46

TABLE XII–9—SUMMARY OF HOUSEHOLD-LEVEL ANNUAL COSTS FOR SYSTEMS TREATING TO COMPLY WITH THE MCL AT 18 μg/L—Continued

[2017$]

Cost range	3% Discount (UCMR 1) [1]	7% Discount (UCMR 1) [1]	3% Discount (national) [1]	7% Discount (national) [1]
Max	72	84	72	84

Source: (USEPA, 2019a).

[1] National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

TABLE XII–10—TOTAL AND ANNUALIZED BENEFITS OF AVOIDED LOST IQ DECREMENTS AT 18 μg/L

[Millions; 2017$]

Korevaar β distribution	Annual delta IQ		UCMR 1		National [1]	
	UCMR 1	National [1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	3.65	0.62	3.68	0.62
Lower	54	55	0.80	0.13	0.80	0.14

Source: (USEPA, 2019a).

[1] The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 μg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% × 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 μg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 μg/L, Table XII–11 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII–12 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII–13 summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

TABLE XII–11—SUMMARY OF TOTAL ANNUALIZED COSTS AT MCL OF 90 μg/L

[Millions; 2017$]

Cost component	3% discount	7% discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs [1]	5.93	6.37
Drinking Water Systems Costs Subtotal	6.42	6.89
State Administration Costs	3.09	3.20
Total Costs	9.51	10.10

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.

[1] Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (*e.g.,* well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

TABLE XII–12—SUMMARY OF HOUSEHOLD-LEVEL ANNUAL COSTS FOR SYSTEMS TREATING TO COMPLY WITH MCL AT 90 μg/L

[2017$]

Cost range	3% Discount	7% Discount
Minimum	$65	$76
Average	65	76
Maximum	65	76

Source: (USEPA, 2019a). There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 μg/L because treatment costs to meet an MCL of 90 μg/L are lower than the costs to meet an MCL of 56 μg/L.

TABLE XII–13—SUMMARY OF TOTAL ANNUALIZED BENEFITS OF AVOIDED LOST IQ DECREMENTS AT MCL OF 90 μg/L

[Millions; 2017$]

Korevaar β distribution	Annual delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	1.83	0.31
Lower	27	0.40	0.07

Source: (USEPA, 2019a).

Table XII–14 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between an MCL of 56 μg/L and an MCL of 18 μg/L and between an MCL of 90 μg/L and 56 μg/L.

Section 1412(b)(4)(C) of the SDWA requires that when proposing a national primary drinking water regulation, ''the Administrator shall publish a determination as to whether the benefits of the maximum contaminant level justify, or do not justify, the costs.'' The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 μg/L using the best available science and data, the EPA Administrator has determined based upon the available information that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs.

Under these circumstances, Section 1412(b)(6)(A) of the SDWA provides, with exceptions not relevant here, that ''the Administrator *may,* after notice and opportunity for public comment promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits.'' The EPA has evaluated the benefits and costs of alternative MCL values of 18 μg/L and 90 μg/L. However, based upon the available information the Administrator also finds that the benefits of an NPDWR at the alternative MCL values would not justify the resulting rule costs. The alternative MCLs would not increase net benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar. Consistent with the discretion afforded the Agency by SDWA Section 1412(b)(6)(A) to decide whether or not to adjust an MCL to a level where the benefits justify the costs, the EPA is however proposing, and may finalize, the MCL of 56 μg/L notwithstanding the Agency's determination that benefits would not justify the costs.

TABLE XII–14—COMPARISON OF ANNUAL COSTS AND BENEFITS BY MCL

[Millions; 2017$]

MCL value	Cost 3% discount	Benefit 3% discount	Cost 7% discount	Benefit 7% discount
UCMR 1:				
90 μg/L	$9.51	$0.40–$3.26	$10.10	$0.07–$0.55
56 μg/L	9.67	0.44–3.57	10.28	0.07–0.60
18 μg/L	15.95	0.80–6.50	16.88	0.13–1.10
Incremental (from 90 μg/L to 56 μg/L)	0.16	0.04–0.31	0.18	0.0–0.05
Incremental (from 56 μg/L to 18 μg/L)	6.28	0.36–2.93	6.60	0.06–0.50
National:				
90 μg/L	9.51	0.40–3.26	10.10	0.07–0.55
56 μg/L [1]	9.67	0.44–3.57	10.28	0.07–0.60
18 μg/L	16.95	0.80–6.56	17.96	0.14–1.11
Incremental (from 90 μg/L to 56 μg/L)	0.16	0.04–0.31	0.18	0.0–0.05
Incremental (from 56 μg/L to 18 μg/L)	7.28	0.36–2.99	7.69	0.07–0.51

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.

[1] For the proposed MCL of 56 μg/L and the alternative MCL of 90 μg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 μg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA has presented an extensive discussion of the uncertainties in the key analyses informing this proposal in the uncertainty section of the MCLG Approaches Report and the uncertainties section of the Economic Analysis document (*USEPA, 2018b; USEPA, 2019a*). A summarized description of these uncertainties are presented below.

A. Uncertainty in the MCLG Derivation

Each input into the analysis to inform the MCLG is a decision point associated with uncertainty. There is uncertainty in different aspects of the BBDR model, ranging from structural and functional relationships to specific parameter values for early pregnancy. There are very few data available to calibrate the pharmacokinetic aspects of the model, particularly at the life stage of interest. Also, the BBDR model does not explicitly consider the effect of the presence of other goitrogens (*e.g.,* thiocyanate, nitrate) or effects of thyroid disease states. Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function

each have their own uncertain features. Additional uncertainty is introduced by linking the BBDR model estimates of maternal fT4 to altered neurodevelopment in offspring. None of the studies used to evaluate potential adverse neurodevelopmental outcomes in offspring born to hypothyroxinemic mothers was performed in the U.S. None of the studies measured perchlorate exposure. Not all the studies measured iodide levels in the study populations. The state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. There are numerous indices used to assess neurodevelopmental impacts and there is some uncertainty regarding the selection of IQ as the critical endpoint for setting the MCLG.

A recently published paper evaluating the EPA's BBDR model and MCLG Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al., 2019).

B. Uncertainty in the Economic Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2019a). Table XIII–1 provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

TABLE XIII–1—SOURCES OF UNCERTAINTY IN ECONOMIC ANALYSIS

Description	Potential effect [1]
Baseline Occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water).	± (benefits and costs will change in the same direction).
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 μg/L or 90 μg/L and that one small system would exceed 18 μg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than the MCLs that are not captured in the national extrapolation results.	− (benefits and costs will change in the same direction).
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction).
Benefits Analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum.	± (benefits only).
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4.	− (benefits only).
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only).
The EPA used a 90th percentile water intake rate to derive the MCLG and the dose-response equations for the benefits analysis. This approach results in a protective MCLG value, but may overstate intake for the benefits analysis [2].	+ (benefits only).
The IQ valuation uses estimates that the EPA derived using the same approach as Salkever (1995). Results from other IQ valuation studies might result in higher or lower benefit estimates.	± (benefits only).
The benefits analysis is based on a single health endpoint and the value of the endpoint is based solely on lost earnings.	− (benefits only).
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor—treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction).
The EPA assumed that all entry points requiring treatment would implement ion exchange, which may overestimate costs if non-treatment is an option for one or more entry points or underestimate costs if site-specific conditions result in higher costs at one or more entry points.	± (costs only).
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only).
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	− (costs only).
The EPA assumed that 90% of ground water systems and 40% of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only).

[1] A "−" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, *i.e.,* benefits and/or costs could be underestimated or overestimated.

[2] The EPA did not include a perchlorate dietary dose in the benefits analysis, which would be unchanged between baseline and proposed MCL scenarios if many areas do not irrigate with drinking water. For people who obtain a significant portion of their fruit, vegetables, and milk from areas irrigated with the water from the same sources as the drinking water, we would expect their exposure may drop with the reduction of perchlorate in food products used locally. Because of this and the natural log form of the IQ response function, this approach may slightly understate the avoided IQ decrement estimates.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al., 1991; Pop et al., 1999; Pop et al., 2003; Kooistra et al., 2006)" (p. 10, SAB for the U.S. EPA, 2013). The EPA's literature review identified potential relationships between maternal thyroid hormone alterations and the risk of schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include risks associated with effects of thyroid disorders in adults, including cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints are not monetized in this benefits analysis. The assumptions used to account for the previously mentioned variability of the BBDR model inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above may result in an overestimate of the monetized benefits. Because IQ is a surrogate for broad range of potential neurodevelopmental risks, it is unclear whether the analysis as a whole over- or under-estimates the monetized benefits of a reduction of perchlorate in drinking water.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues will be especially helpful to the EPA in developing a final rule. The EPA specifically requests comment on the following topics.

- The adequacy and uncertainties of the BBDR model developed by the EPA to predict thyroid hormone level changes caused by perchlorate exposure to pregnant women with low iodide intake, including the model and model parameters and assumptions (Section III and Approaches Report).
- The adequacy and uncertainties of the EPA's review and application of the epidemiologic literature to quantify the relationship between thyroid hormone changes in pregnant women and neurodevelopmental effects including the assumptions, the selection of the approach used, and the study used (Section III and Approaches Report).
- The adequacy and uncertainties of the methodology to derive the MCLG including points of departure, assumptions, uncertainty factor, and relative source contribution (Section III and Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water).
- The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.
- The feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.
- The adequacy of the underlying assumptions and analysis of occurrence (Section VI).
- The costs and availability of Treatment Technologies (Section X).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate costs and describe unquantified costs including the estimates of monitoring frequency, likelihood of systems receiving a monitoring waiver, the administrative labor rate and the operator labor rate. (Section XII and the Health Risk Reduction Cost Analysis).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate benefits and describe unquantified benefits (Section XII and the Health Risk Reduction Cost Analysis).
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's finding in accordance with Section 1412(b)(4)(C) of the SDWA that the benefits of the proposed 56 µg/L MCL for perchlorate do not justify the costs, and the information that supports that determination as described in Section XII of this notice.
- The Administrator's proposal to, consistent with the discretion afforded him by SDWA Section 1412(b)(6)(A), adopt an MCL of 56 µg/L notwithstanding the Agency's SDWA Section 1412(b)(4)(C) determination that the benefits of the MCL would not justify its costs.
- The Agency's conclusion that no alternative MCL, including the alternative MCL values of 18 µg/L and 90 µg/L discussed above, would "maximize health risk reduction benefits at a cost that is justified by the benefits" and the information and analytical approaches used to arrive at that conclusion. The EPA is especially interested in comments suggesting other approaches to deriving an MCL for which the benefits justify the costs.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II–C, Regulatory History) based on several factors. First, the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern [17] and suggest that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate, but the available data indicates that very few would find it at levels of public health concern. Specifically, perchlorate occurrence information suggests that at an MCL of 56 µg/L only 2 systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Even at an MCL of 18 µg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. Only one system would exceed the alternative MCL of 90 µg/L.

The EPA notes that in 2008, the EPA stated in its preliminary regulatory determination that perchlorate did not occur with a frequency and at levels of public health concern in public water systems based upon the health effects and occurrence information available at that time, which indicated that 0.8% of public water system had perchlorate at levels exceeding the HRL of 15 µg/L. The EPA also stated that there was not a meaningful opportunity for a NPDWR to reduce health risks based upon the estimates at that time that 0.9 million

[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or 90 µg/L, which are the possible levels expected to cause adverse human health effects.

people had perchlorate levels above the HRL.

The EPA further notes that the Agency has previously determined CCL1 and CCL2 contaminants did not occur with frequency at levels of public health concern when the percentage of water systems exceeding the HRL were greater than the frequency of perchlorate occurrence level at the proposed MCL (0.004% of all water systems in the U.S.). For example, in 2003 the EPA determined that aldrin did not occur with a frequency and at levels of public health concern based upon data that showed 0.2% of water systems had aldrin at levels greater than the HRL. The EPA also concluded that there was not a meaningful opportunity for health risk reduction for persons served through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 1 million people (USEPA, 2003). In 2008 the EPA determined that DCPA Mono- and Di-Acid degradates did not occur with a frequency and at levels of public health concern based on data that showed 0.03% of water systems exceeded the HRL. The EPA also included that there was not a meaningful opportunity for health risk reduction through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 100,000 people (USEPA, 2008e).

SDWA Section 1412(b)(1)(A)(iii) states that the determination regarding the meaningful opportunity is "in the sole judgement of the Administrator" and therefore there may be other factors that contribute to this determination for any given contaminant.

If, after consideration of public comment, the EPA withdraws the perchlorate regulatory determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using its SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authorities, as appropriate. The EPA also requests comments on what guidance it could provide the public if the regulatory determination for perchlorate is withdrawn.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule* (*USEPA, 2019a*) is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in the EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq.* The information collection requirements are not enforceable until OMB approves them.

The monitoring information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule including adopting the NPDWR into state regulations, providing training to state and PWS employees, updating their monitoring data systems, and reviewing system monitoring data and waiver requests. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) would not begin until after Year 3 due to the proposed effective date of this rule.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to the EPA at the public docket established for this rule, which includes the ICR, Docket ID No. EPA–HQ–OW–2018–0780. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to *OIRA_submission@omb.eop.gov*, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE **FEDERAL REGISTER**]. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public

water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the **Federal Register**, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 7 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a). Table XII–1 and Table XII–2 show the annual compliance costs of the proposed rule on the small entities by system size for public and private systems, respectively. Based on a comparison of annual costs with annual revenue estimates, the EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2019a).

TABLE XII–1—ANNUALIZED MONITORING AND ADMINISTRATIVE COSTS AS A PERCENTAGE OF AVERAGE ANNUAL REVENUE FOR SMALL PUBLIC CWSS BY SIZE CATEGORY

Size category	Average annual revenues [a]	3% Discount [b]	7% Discount [b]
Population served <100	$224,248	$88 (0.04%)	$94 (0.04%)
Population served 101–500	197,315	88 (0.04%)	94 (0.05%)
Population served 501–3,300	202,382	88 (0.04%)	94 (0.05%)
Population served 3,301–10,000	1,092,187	88 (0.01%)	94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA–HQ–OW–2018–0780).
[a] Based on the CWSS (USEPA, 2009c Table 65) and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers (BLS, 2018a). Revenues include all sources of revenue including water revenue, non-water revenue, and municipal transfers to water systems.
[b] Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

TABLE XII–2—ANNUALIZED MONITORING AND ADMINISTRATIVE COSTS AS A PERCENTAGE OF AVERAGE ANNUAL REVENUE FOR SMALL PRIVATE CWSS BY SIZE CATEGORY

Size category	Average annual revenues [a]	3% Discount [b]	7% Discount [b]
Population served <100	$139,911	$88 (0.06%)	$94 (0.07%)
Population served 101–500	351,974	88 (0.03%)	94 (0.03%)
Population served 501–3,300	254,706	88 (0.03%)	94 (0.03%)
Population served 3,301–10,000	951,692	88 (0.01%)	94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA–HQ–OW–2018–0780)
[a] Based on the CWSS (USEPA, 2009c Table 65) and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers (BLS, 2018a). Revenues include all sources of revenue including water revenue and non-water revenue.
[b] Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector.

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the

funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a webinar with interested tribes on February 28, 2012, to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012a). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children From Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation—offspring of pregnant women exposed to perchlorate during the first trimester—and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2019a) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use

This rule is not a "significant energy action" as defined in Executive Order 13211, "Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use" (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995 and 1 CFR Part 51

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. The EPA methods 314.0, 314.1, 314.2, 331.0, and 332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice. The EPA has made, and will continue to make, these documents generally available through *www.regulations.gov* and at the U.S. Environmental Protection Agency Drinking Water Docket, William Jefferson Clinton West Building, 1301 Constitution Ave. NW, Room 3334, Washington, DC 20460, call (202) 566–2426.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation. The Director of the Federal Register approved the voluntary consensus standards incorporated by referenced in § 141.23 of the proposed regulatory text as of April 11, 2007.

K. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse

human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

XVII. Consultations With the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4–5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC, 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (USEPA, 2012; NRC, 2005). On May 29, 2013, the EPA received significant input from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (USEPA, 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking process for perchlorate (USEPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (USEPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (*i.e.,* iodide uptake inhibition by the thyroid) (USEPA 2013a). Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). The EPA provided information to HHS officials on the draft proposed perchlorate regulation and considered HHS input as part of the interagency review described in section XVII.A.

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List of Subjects

40 CFR Part 141

Chemicals, Incorporation by reference, Indians—lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

40 CFR Part 142

Administrative practice and procedure, Chemicals, Indians—lands, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated: May 23, 2019.

Andrew R. Wheeler,

Administrator.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR parts 141 and 142 as follows:

PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS

■ 1. The authority citation for part 141 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g–1, 300g–2, 300g–3, 300g–4, 300g–5, 300g–6, 300j–4, 300j–9, and 300j–11.

■ 2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l) to read as follows:

Subpart A—General

§ 141.6 Effective dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

* * * * *

(l) The regulations contained in the revisions to §§ 141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)–(2), 141.23(k)(1)–(3), 141.23(k)(3)(ii), 141.51(b), 141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [DATE OF PUBLICATION OF FINAL RULE IN THE **FEDERAL REGISTER**].

■ 3. Amend § 141.23 by:

■ a. In paragraph (a)(4)(i) table:

■ i. Revising the table heading; and

■ ii. Adding an entry for "Perchlorate" in alphabetical order;

■ b. In paragraph (a)(5), after the text "nickel," adding the text "perchlorate,";

■ c. In paragraph (c), after the text "nickel," adding the text "perchlorate,";

■ d. Adding paragraph (c)(10);

■ e. In paragraph (f)(1), after the text "nickel," adding the text "perchlorate,";

■ f. In paragraphs (i)(1) and (2), after the text "nickel," adding the text "perchlorate,";

■ g. Revising paragraph (i)(3);

■ h. In paragraph (k)(1):

■ i. Revising the introductory text; and

■ ii. In the table, adding the table designation, redesignating entries 21 through 26 as 22 through 27, and adding a new entry 21;

■ i. In paragraph (k)(2):

■ i. In the introductory paragraph, after the text "nitrite," adding the text "perchlorate,"; and

■ ii. In the table, adding the table designation and adding, in alphabetical order, an entry for "Perchlorate";

■ j. In paragraph (k)(3):

■ i. In the introductory paragraph, after the text "nitrite" adding the text ", perchlorate,"; and

■ ii. In paragraph (ii) table, adding the table designation, and adding in alphabetical order, an entry for "Perchlorate";

The revisions and additions read as follows:

Subpart C—Monitoring and Analytical Requirements

§ 141.23 Inorganic chemical sampling and analytical requirements.

* * * * *

(a) * * *

(4) * * *

(i) * * *

TABLE 1 TO PARAGRAPH (a)(4)(i)— DETECTION LIMITS FOR INORGANIC CONTAMINANTS

[Composited samples]

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*	*	* *	* * *
Perchlorate	0.056	Ion Chromatography	0.00053.
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection.	0.00003.
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection.	0.000012–0.000018.
		Liquid Chromatography Electrospray Ionization Mass Spectrometry.	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM]).
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry.	0.00002.
*	*	* *	* * *

* * * * *

(c) * * *

(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023 and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all

sampling points between January 1, 2026 and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023 and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution system may use the monitoring data from the compliance monitoring period that began between January 1, 2020 and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

* * * * *

(i) * * *

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph (f)(1) of this section and compliance shall be based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph (f)(2) of this section and compliance shall be based on the average of the initial and confirmation sample.

* * * * *

(k) * * *

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to Subpart C of this part, or their equivalent as determined by the EPA. Criteria for analyzing arsenic, barium, beryllium, cadmium, calcium, chromium, copper, lead, nickel, selenium, sodium, and thallium with digestion or directly without digestion, and other analytical test procedures are contained in Technical Notes on Drinking Water Methods, EPA–600/R–94–173, October 1994. This document is available from the National Service Center for Environmental Publications (NSCEP), P.O. Box 42419, Cincinnati, OH 45242–0419 or *http://www.epa.gov/nscep/.*

TABLE 2 TO PARAGRAPH (k)(1)

Contaminant	Methodology [13]	EPA	ASTM [3]	SM [4] (18th, 19th ed.)	SM [4] (20th ed.)	SM Online [22]	Other
*	*	*	*	*	*		*
21. Perchlorate	Ion Chromatography	[23] 314.0					
	Inline Column Concentration/ Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection.	[24] 314.1					
	Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection.	[25] 314.2					
	Liquid Chromatography Electrospray Ionization Mass Spectrometry.	[26] 331.0					
	Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry.	[27] 332.0					
*	*	*	*	*	*		*

[3] *Annual Book of ASTM Standards,* ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, *http://www.astm.org.;* Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

[4] *Standard Methods for the Examination of Water and Wastewater,* American Public Health Association, 800 I Street NW, Washington, DC 20001–3710; *Standard Methods for the Examination of Water and Wastewater,* 18th edition (1992); *Standard Methods for the Examination of Water and Wastewater,* 19th edition (1995); *Standard Methods for the Examination of Water and Wastewater,* 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

[13] Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (*i.e.,* no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559–90D, unless multiple in-furnace depositions are made.

* * * * * * *

[22] Standard Methods Online, American Public Health Association, 800 I Street NW, Washington, DC 20001, available at *http://www.standardmethods.org.* The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

[23] Determination of Perchlorate in Drinking Water Using Ion Chromatography (Revision 1.0, USEPA, 1999a).

[24] Determination of Perchlorate in Drinking Water Using Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection (Revision 1.0, USEPA, 2005b).

[25] Determination of Perchlorate in Drinking Water Using Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection (USEPA, 2008c).

[26] Determination of Perchlorate in Drinking Water by Liquid Chromatography Electrospray Ionization Mass Spectrometry'' (Revision 1.0, USEPA, 2005c).

[27] Determination of Perchlorate in Drinking Water by Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry'' (USEPA, Revision 1.0, 2005d).

The approved compliance methods for determining perchlorate in drinking water listed in table 1 to paragraph (k) of this section, are incorporated by reference. The Director of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies of the material incorporated by reference in this paragraph (k) may be inspected at the U.S. Environmental Protection Agency, EPA Headquarters Library, in the Water Docket, at the EPA Docket Center (EPA/DC), EPA WJC West, Room 3334, 1301 Constitution Ave. NW, Washington, DC 20460. If you wish to obtain this material from the EPA Docket Center, call (202) 566–2426. Copies of this material also may be inspected at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call (202) 741–6030, or go to *www.archives.gov/federal-register/cfr/ibr-locations.html.*

* * * * *

(2) * * *

TABLE 3 TO PARAGRAPH (k)(2)

Contaminant	Preservative [1]	Container [2]	Time [3]
*	*	*	*
Perchlorate [7]	4 °C	P or G	28 days.
*	*	*	*

[1] For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2] P = plastic, hard or soft; G = glass, hard or soft.

[3] In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

* * * * * * *

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

* * * * *

(3) * * *

(ii) * * *

TABLE 4 TO PARAGRAPH (k)(3)(ii)

Contaminant	Acceptance limit
*	*
Perchlorate	±20% at ≥0.004 mg/L.
*	*

* * * * *

■ 4. In § 141.51 amend paragraph (b) by adding a designation to the table and by adding in alphabetical order, an entry for ''Perchlorate'' to read as follows:

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

§ 141.51 Maximum contaminant level goals for inorganic contaminants.

* * * * *

(b) * * *

TABLE 1 TO PARAGRAPH (b)

Contaminant	MCLG (mg/l)
*	*
Perchlorate	0.056
*	*

* * * * *

■ 5. Amend § 141.60 by adding paragraph (b)(5) to read as follows:

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§ 141.60 Effective dates.

* * * * *

(b) * * *

(5) The effective date for § 141.62(b)(17) is [DATE OF PUBLICATION OF FINAL RULE IN THE **FEDERAL REGISTER**].

■ 6. Amend § 141.62 by:

■ a. In the table in paragraph (b), adding a designation to the table and an entry for ''(17) Perchlorate'' at the end of the table;

■ b. In the table in paragraph (c), adding a designation to the table, an entry for ''Perchlorate'' in alphabetical order, and an entry ''14 = Biological Treatment'' under the undesignated heading entitled ''Key to BATs; and

■ c. Adding paragraph (e).

The revisions and additions read as follows:

§ 141.62 Maximum contaminant levels for inorganic contaminants.

* * * * *

(b) * * *

TABLE 1 TO PARAGRAPH (b)

Contaminant	MCL (mg/l)
* * * * *	
(17) Perchlorate	0.056

(c) * * *

TABLE 2 TO PARAGRAPH (c)—BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(B)

Chemical name	BAT(s)
* * * * *	
Perchlorate	5, 7, 14.
* * * * *	

* * * * *

Key to BATs in Table

* * * * *

14 = Biological Treatment

* * * * *

(e) The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000 persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

TABLE 3 TO PARAGRAPH (e)—SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTS) FOR PERCHLORATE

Small system compliance technology	Affordability for listed small system categories
Ion exchange	All size categories.
Reverse osmosis (point of use).	All size categories.

■ 7. Amend Appendix A to Subpart O of Part 141 table, under "Inorganic contaminants", by adding an entry for "Perchlorate" in alphabetical order to read as follows:

Subpart O—Consumer Confidence Reports

APPENDIX A TO SUBPART O OF PART 141—REGUATED CONTAMINANTS

Contaminant (units)	Traditional MCL in mg/L	To convert for CCR, multiply by	MCL in CCR units	MCLG	Major sources in drinking water	Health effects language
*	*	*	*	*	*	*
Inorganic contaminants						
Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*	*	*	*	*	*	*

■ 8. Amend Appendix A to Subpart Q of Part 141 table, under "B. Inorganic contaminants", by adding an entry for "Perchlorate" in alphabetical order to read as follows:

Subpart Q—Public Notification of Drinking Water Violations

* * * * *

APPENDIX A TO SUBPART Q OF PART 141—NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE [1]

Contaminant	MCL/MRDL/TT violations [2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation
*	*	*	*	*
B. Inorganic Chemicals (IOCs)				
*	*	*	*	*
14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1).

APPENDIX A TO SUBPART Q OF PART 141—NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE [1]—Continued

Contaminant	MCL/MRDL/TT violations [2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation
*	*	*	*	*	*	*

[1] Violations and other situations not listed in this table (*e.g.*, failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (*e.g.*, Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

* * * * *

■ 9. Amend Appendix B to Subpart Q of Part 141 table, under "C. Inorganic contaminants", by adding an entry for "Perchlorate" in alphabetical order to read as follows:

APPENDIX B TO SUBPART Q OF PART 141—STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

Contaminant	MCLG [1] mg/L	MCL [2] mg/L	Standard health effects language for public notification
*	*	*	*	*	*	*
C. Inorganic Chemicals (IOCs)			
*	*	*	*	*	*	*
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*	*	*	*	*	*	*

[1] MCLG—Maximum contaminant level goal.
[2] MCL—Maximum contaminant level.

PART 142—NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION

■ 10. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g–1, 300g–2, 300g–3, 300g–4, 300g–5, 300g–6, 300j–4, 300j–9, and 300j–11.

■ 11. In § 142.62 amend the table in paragraph (b) by adding a designation to the table, an entry for "Perchlorate" in alphabetical order; and an entry "13 = Biological Treatment" under the undesignated heading entitled "Key to BATs".

Subpart G—Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

* * * * *

§ 142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

* * * * *

(b) * * *

TABLE 1 TO PARAGRAPH (b)—BAT FOR INORGANIC COMPOUNDS LISTED IN § 141.62(b)

Chemical name	BAT(s)
*	*	*	*
Perchlorate	5, 7, 14
*	*	*	*

TABLE 1 TO PARAGRAPH (b)—BAT FOR INORGANIC COMPOUNDS LISTED IN § 141.62(b)—Continued

Chemical name	BAT(s)
*	*	*	*

* * * * *

Key to BATs in Table

* * * * *

13 = Biological Treatment

* * * * *

[FR Doc. 2019–12773 Filed 6–25–19; 8:45 am]

BILLING CODE 6560–50–P

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 5/23/2019 2:42:43 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]
CC: Lousberg, Macara [Lousberg.Macara@epa.gov]; Nickerson, William [Nickerson.William@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]; Manibusan, Mary [Manibusan.Mary@epa.gov]; Adams, Darryl [Adams.Darryl@epa.gov]
Subject: RE: Draft Perchlorate Signature /Roll out schedule:
Attachments: Final Version for Signature NPDWR Proposed Perchlorate Rule 5-23-19.docx

Hi,

Attached is the Final Version for signature. Thank You for assisstance on this effort.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Thursday, May 23, 2019 10:34 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>; Adams, Darryl <Adams.Darryl@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

All: We have just concluded discussions with OMB and they are opening ROCIS for clearance of the package (that I sent separately to Darryl to and Mary). Sam will send the clean versions forward for signature shortly. Thank you all for your continued focus on this issue and for helping us to achieve this goal.

From: Burneson, Eric
Sent: Wednesday, May 22, 2019 5:36 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>;

Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; 'Joe Tiago (Tiago.Joseph@epa.gov)' <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <manibusan.mary@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

All:
I just had a conversation with OMB and they estimate that within the next hour they will be transmitting minor edits to the FRN and that are not substantive in nature. They also expect to let us know that they will be opening ROCIS at that time to receive the final version for close out of OMB review. They noted that there are some issues being raised by SBA that could impede that timeline but they expect those issues will be resolved.

I also learned that the A.O. is still anticipating signature by 10:00 am tomorrow.

Thanks for your continued work on this important project.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Monday, May 20, 2019 3:54 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; 'Joe Tiago (Tiago.Joseph@epa.gov)' <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Manibusan, Mary <manibusan.mary@epa.gov>
Subject: RE: Draft Perchlorate Signature /Roll out schedule:

All:
Attached please find an updated timeline to reflect some adjustments based upon when OMB is available for discussion tomorrow. We have informed OMB our intended timeline for signature and they indicated that it was extremely compressed and that they could not guarantee clearance in time but that they would do what they could to expedite completion of the interagency review. OMB has been forwarding the comments from other Federal Agencies today but we are still awaiting the OMB consolidated mark up.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Friday, May 17, 2019 12:39 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Joe Tiago (Tiago.Joseph@epa.gov) <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Draft Perchlorate Signature /Roll out schedule:

All: We have received notice that the already short time frame for signature for the perchlorate proposal needs to be shortened to assure signature before 1:00 pm on Thursday May 23. Attached please find a timeline of the actions that must take place between receipt of Inter Agency comments from OMB (expected COB on 5/20) and the new signature deadline we have been asked to work against. Can you please review the attached and let me know if there are significant steps that will require time not anticipated in the attached timeline.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, the EPA is requesting comment on three alternatives: 1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18

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μg/L), 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 μg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011, determination to regulate perchlorate in drinking water based on new information that indicates that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and there may not be a meaningful opportunity for health risk reduction through a drinking water regulation. Under this last alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at [HYPERLINK "http://www.regulations.gov"]. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not

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consider comments or comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit [HYPERLINK "http://www2.epa.gov/dockets/commenting-epa-dockets"].

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This proposed rule is organized as follows:

I. General Information

A. What is the EPA Proposing?

B. Does This Action Apply to Me?

II. Background

A. What is Perchlorate?

B. Statutory Authority

C. Statutory Framework and Regulatory History

III. Assessment and Modeling of the Health Effects of Perchlorate

A. 2008 Preliminary Regulatory Determinations

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

C. Science Advisory Board Recommendations

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D. Perchlorate Model Development and Peer Reviews

E. Sensitive Population for Deriving MCLG

F. BBDR Model Specification for the Sensitive Population

G. Epidemiological Literature

H. Identifying a Point of Departure for Developing the MCLG

I. Translate PODs to RfDs

J. Translate RfD into an MCLG

IV. Maximum Contaminant Level Goal and Alternatives

V. Maximum Contaminant Level and Alternatives

VI. Occurrence

VII. Analytical Methods

VIII. Monitoring and Compliance Requirements

A. What are the Monitoring Requirements?

B. Can States Grant Monitoring Waivers?

C. How are System MCL Violations Determined?

D. When Must Systems Complete Initial Monitoring?

E. Can Systems Use Grandfathered Data to Satisfy the Initial Monitoring Requirement?

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

B. What are the Public Notification Requirements?

X. Treatment Technologies

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A. What are the Best Available Technologies?

B. What are the Small System Compliance Technologies?

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

B. What are the State Record Keeping Requirements?

C. What are the State Reporting Requirements?

XII. Health Risk Reduction Cost Analysis

A. Identifying Affected Entities

B. Method for Estimating Costs

C. Method for Estimating Benefits

D. Comparison of Costs and Benefits

XIII. Uncertainty Analysis

A. Uncertainties in the MCLG Derivation

B. Uncertainties in the Economic Analysis

XIV. Request for Comment on Proposed Rule

XV. Request for Comment on Potential Regulatory Determination Withdrawal

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

C. Paperwork Reduction Act

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D. Regulatory Flexibility Act (RFA)

E. Unfunded Mandates Reform Act

F. Executive Order 13132: Federalism

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use

J. National Technology Transfer and Advancement Act of 1995

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of 56 µg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 µg/L.

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The EPA is proposing an NPDWR for perchlorate in accordance with its February 11, 2011, (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is soliciting comment on two alternative MCLG/MCL values of 18 µg/L and 90 µg/L respectively. Third, in light of new considerations that have come to the EPA's attention since it issued its positive regulatory determination in 2011, including information on lower levels of occurrence of perchlorate than the EPA had previously believed to exist and new analysis of the concentration that represents a level of health concern, this action also discusses and requests comment on an alternative action under which the EPA would withdraw its 2011 determination to regulate perchlorate. Under this alternative, there would be no MCLG or NPDWR for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems

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State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a

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frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Statutory Framework and Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five

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years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water system. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems (CWS) and non-transient, non-community water systems (NTNCWS). The UCMR collects data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556) which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999, 2000b).

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule knows as the sodium/iodide symporter (NIS), which may lead to decreases in two hormones, thyroxine (T3) and triiodothyronine (T4) and increases in thyroid-stimulating hormone (TSH) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are “the fetuses of pregnant women who might have hypothyroidism or iodide deficiency” (p. 178). The EPA established a reference dose (RfD) consistent with the recommended National Research Council RfD of 0.7 µg/kg/day for perchlorate. The reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-

parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA,

2008a)","plainCitation":"(USEPA,
2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal
Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-

2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Based primarily on the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In January 2009 the EPA published an interim health advisory for perchlorate of 15 µg/L, consistent with the HRL derivation for perchlorate of 15 µg/L described above. Health Advisories are non-enforceable and non-regulatory and provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health Advisories provide the public, including the most sensitive populations, with a margin of protection from a lifetime of exposure. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information (74 FR 41883; USEPA, 2009a). After careful consideration of public comments on

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the October 2008 and August 2009 notices, on February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011a). The Agency stated then that when considering the alternative HRL benchmarks described in the 2009 notice, the likelihood of perchlorate to occur at levels of concern had significantly increased in comparison to the levels described on the 2008 preliminary negative determination. The EPA concluded that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally described in the 2008 notice.

In its 2011 determination, the Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data for systems in California and Massachusetts using state

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compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than October 31, 2018, and finalize an NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water was later extended to May 28, 2019. The consent decree is available in the docket for today's proposed rule.

III. Assessment and Modeling of the Health Effects of Perchlorate

Perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the NIS (ATSDR, 2008; Greer et al., 2002; NRC, 2005; SAB 2013; Taylor et al., 2013). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB for the U.S. EPA, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB for the U.S. EPA, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

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The mode of action of perchlorate toxicity has been proposed as follows: exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland through the NIS (NRC, 2005; SAB for the U.S. EPA, 2013). A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that T3 and T4 require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased TSH, the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"eF6zWm7L","properties":{"formattedCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","plainCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","noteIndex":0},"citationItems":[{"id":428,"uris":["http://zotero.org/groups/945096/items/UIANA947"],"uri":["http://zotero.org/groups/945096/items/UIANA947"],"itemData":{"id":428,"type":"bill","title":"Toxicological Profile for Perchlorates","author":[{"family":"ATSDR","given":""}],"issued":{"date-parts":[["2008"]]}}},{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid tormone levels in adolescent and adult men and women living in the United States","container-title":"Environmental Health

Perspectives","page":"1865-1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]}}},{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the national health and nutrition examination survey 2007-8","container-title":"Environmental research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors ...","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID:

23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]}}},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy, including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L.

Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth

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N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to decrements in neurocognitive function in offspring (Alexander et al., 2017; Thompson et al., 2018; Wang et al., 2016). There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate's mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in

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[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

sensitive populations. Therefore, based on the known mode of action of perchlorate the Agency estimated potential health risks using a novel approach suggested by the EPA's Science Advisory Board (SAB for the U.S. EPA, 2013). The EPA's approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of T3 and T4, and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency). Based on these findings, the NRC recommended a reference dose of 0.7 µg/kg/day.

Based on NRC's analysis, the EPA established a perchlorate reference dose (RfD) of 0.7 µg/kg/day in 2005 (USEPA, 2005). This value was based on a no observed effect level (NOEL) of 7 µg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

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As discussed above, in 2008, the EPA derived an HRL of 15 µg/L using the RfD of 0.7 µg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (i.e., food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the subpopulation identified by the NAS as likely the most sensitive to the effects of perchlorate exposure, fetuses.

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the EPA developed alternative HRLs for other sensitive populations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 µg/L to 47 µg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

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C. Science Advisory Board Recommendations

As required by Section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

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This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically free T4 (fT4)) that are associated with maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Reviews

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, i.e., breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). In addition to estimating effects on breast fed infants, several reviewers recommended that the EPA shift the primary focus of its analysis to modeling the exposure implications to the fetus during early pregnancy. This was based on the knowledge that fetuses lack a functioning thyroid gland until approximately 16 gestational weeks and the substantial epidemiological evidence linking

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early pregnancy low fT4 levels with adverse neurodevelopmental outcomes [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. Specifically, the SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: “the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women” (SAB for the U.S. EPA, 2013, p. 19).

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The EPA considered all recommendations from the 2017 peer review. The previously developed BBDR model describing perchlorate's effects in the third trimester (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b) was calibrated only for that phase of pregnancy, not for the first trimester, and lacked a description of TSH signaling (feedback) that becomes significant as individuals become hypothyroxinemic or hypothyroid. In particular, this signaling was considered necessary to accurately predict responses of women with very low iodine intake, which was also part of the 2017 peer review recommendations. Therefore, the Lumen et al., (2009b) model needed to be revised to address these recommendations and the EPA implemented those changes needed to increase the scientific rigor of the model and modeling results. These modifications include:

- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in January 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches in the draft *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (MCLG Approaches Report) to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using

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evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018). The 2018 peer review identified a variety of strengths and limitations of the modeling (to be discussed in more detail later in this notice). The peer review panel was largely supportive of the efforts described in the MCLG Approaches Report, as evidenced by the following from the peer review final report:

> *Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).*

The EPA also presented an alternative, population-based approach evaluating the shift in the proportion of the population that would fall below a hypothyroxinemic cut point, given exposure to perchlorate (Section 7 of the MCLG Approaches Report). This approach does not directly connect the BBDR output to a neurodevelopmental endpoint. However, for pregnant women in early pregnancy, this shift could be related to avoiding an increase in the population of offspring's risk of adverse neurodevelopmental impacts. The 2018 peer review identified strengths associated with this approach, including

> *1) the central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; 2) this approach encompasses a variety of adverse*

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neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and 3) this approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an adverse neurodevelopmental effect. (External Peer Reviewers for U.S. EPA, 2018, p. 7)

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for an MCLG based on this approach to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The peer-review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. The EPA is requesting public comment in Section XIV on the adequacies and uncertainties of the methodology to derive the MCLG including the decision not to pursue this population-based approach for setting the MCLG.

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Based on the comments of the peer reviewers, the EPA's final analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking water (see Figure 1). In summary, because of the known mode of action, the lack of epidemiological studies particularly in the sensitive populations and the direction of the SAB to use a "data-driven approach [which] represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages" (p. 2, SAB 2013 for U.S. EPA), the EPA uses a combination of the BBDR model that simulates perchlorate potential impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail, highlighting each step in which decisions and assumptions were made.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring

[EMBED Visio.Drawing.15]

Note: Process figure does not imply the strength of scientific evidence.

E. Sensitive Population for Deriving MCLG

SDWA 1412(b)(4)(A) requires MCLGs to be set at a concentration in water "at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." SDWA 1412(b)(3)(C)(V) further requires that the EPA "consider the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health

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effects due to exposure to contaminants in drinking water than the general population." The EPA has interpreted these requirements to establish MCLGs that avoid adverse effects within the portions of the population that are at greater risk of adverse effects from exposure to the contaminant. The EPA is proposing an MCLG that is developed to protect the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of an fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The choice of this population is consistent with discussion by the NRC (2005), and the SAB (2013). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-

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number>246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 μg/day). Assuming 2 or 4 μg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 μg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than

[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

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75 µg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there are reports in the scientific literature suggesting that minor perturbations in thyroid hormone levels in the first trimester mother may adversely impact her offspring's neurodevelopment. Specifically, some studies show that children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) have a higher risk of reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Notably these effects are correlated with both degree [ADDIN EN.CITE ADDIN EN.CITE.DATA] and duration [ADDIN EN.CITE <EndNote><Cite><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(Pop et al., 2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-

288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] of maternal hypothyroxinemia [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>`; p. 10</Suffix><DisplayText>(SAB, 2013; p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. This finding is consistent with conclusions by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><Prefix>CalEPA`, </Prefix><Suffix>`; p. 90</Suffix><DisplayText>(CalEPA, 2015; p. 90)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-

id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency (CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

Specifically, two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. [HYPERLINK \l "_ENREF_9" \o "Costeira, 2011 #7"] found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, [HYPERLINK \l "_ENREF_17" \o "Henrichs, 2010 #928"] found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: preterm infants that experience transient

hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB for the U.S. EPA, 2013). Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive lifestage and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and

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- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to many other PBPK models. Because perchlorate does not undergo metabolism in vivo (Clewell et al., 2007), potential uncertainty from this factor of the model is avoided since it does not need to be described.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model estimates serum thyroid hormone levels in the mother at specific gestational weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, to be health protective the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG, thereby protecting both this target sensitive population with an adequate margin of safety and those who are less sensitive with an even larger margin of safety.

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The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al., (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>1160</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-number>1160</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206437">1160</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce,</author><author>Braverman</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice and Research: Clinical Endocrinology and Metabolism</secondary-title><alt-title>Best Pract Res Clin Endocrinol Metab</alt-title><short-title>Best Practice and Research: Clinical Endocrinology and Metabolism</short-title></titles><alt-periodical><full-title>Best Pract Res Clin Endocrinol Metab</full-title></alt-periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates>

<isbn>ISSN 1521-690X
EISSN 1532-1908</isbn><label>755955</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1016/j.beem.2009.08.009</url></related-urls></urls><electronic-resource-num>10.1016/j.beem.2009.08.009</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The EPA selected an iodine intake level of 75 µg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 µg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH

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[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><Pages>332</Pages><DisplayText>(Alexander et al., 2017, p. 332)</DisplayText><record><rec-number>1895</rec-

ranges between 4.51 and 5.41 milli-international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

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number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American journal of obstetrics and gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-title></periodical><pages>62-e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

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TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones[ADDIN EN.CITE ADDIN EN.CITE.DATA]. The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in [REF _Ref517525852 \h * MERGEFORMAT].

Table III-[SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 Levels: Pregnant Women at Gestational Week 13, Assuming Low (75 µg/day) Iodine Intake and with Muted TSH feedback strength[a][]

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)

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5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] pTSH = 0.398; see USEPA, (2018b) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67. All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestation week and did not account for variation in perchlorate and iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (e.g. Blount et al., 2007) and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3). The EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4 for the identified sensitive population, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4 concentrations for women with low fT4 of childbearing age would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. To protect the most sensitive population from adverse effects, the EPA chose to use the 10th percentile from this

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distribution of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population[5].

G. Epidemiological Literature

The SAB recommended that the EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Roman et al., 2013; van Mil et al., 2012). These individual studies showing that maternal hypothyroxinemia is associated with offspring neurodevelopment are also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Additionally, the American Thyroid Association concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

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[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

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The EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes given: 1) the body of scientific literature regarding this association, and 2) the SAB recommendation that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25). Instead, the EPA conducted a "methodologic approach to reviewing the literature" to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. More specifically, the EPA only used studies that had sufficient data to show a quantitative relationship between maternal fT4 and a neurodevelopmental outcome. The EPA acknowledges that by not giving any weight to the studies that did not show a quantitative relationship between fT4 and neurodevelopmental outcomes, the Agency may be overestimating the dose of perchlorate that may be associated with adverse neurodevelopmental outcomes. This is a health protective decision that adds to the margin of safety.

Ultimately, the EPA developed a dose-response function that estimates incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

The specifics of this "methodologic approach to reviewing the literature" follow. First, the EPA identified and screened the available 71 epidemiological studies, which potentially

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pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- compatible with the sensitive life stages identified by the NRC and SAB;
- continuous measure of thyroid hormone values (versus categorical values);
- low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- access to underlying data.

Second, using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40 studies). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia. Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a

[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

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continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior and other outcomes. The EPA notes that by selecting the papers that potentially had dose response data the Agency is deviating from the systematic weight of evidence review approach to identify those studies that the SAB recommended we examine to derive the MCLG.

Third, from these 15 papers five were selected for dose response assessment - four related to cognition[ADDIN EN.CITE ADDIN EN.CITE.DATA] and one related to behavior [ADDIN EN.CITE

<EndNote><Cite><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(Endendijk, Wijnen, Pop, & van Baar, 2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk, J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar, A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories

during pregnancy and child behavioral problems</title><secondary-title>Horm Behav</secondary-title></titles><periodical><full-title>Horm Behav</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-response assessment (e.g., dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al., (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

As laid out for the peer reviewers, for each study that met the criteria identified above for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018b). These relationships

were either presented in the original published paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to assure consideration of the populations likely to be at greater risk from the dose of perchlorate associated with a given change in fT4.

Table III-2 provides a summary of the changes in fT4 predicted to produce a 1, 2, and 3 percent decrease in any given neurodevelopmental effect and corresponding perchlorate doses. The choice of 1, 2, and 3% is based on the analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI). Specifically, a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points) equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively (Endendijk et al., 2017; Finken et al., 2013).

These results provide the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (derived from the epidemiologic literature[7]).

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[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the MCLG Approaches Report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

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Table III-2. Estimated Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopment for the Population of Low-Iodine Intake Women of Reproductive Age Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al., (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1
Korevaar et al., (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8
Pop et al., (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al., (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al., (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al., (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al., (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

H. Identifying a Point of Departure for Developing the MCLG

From the seven analyses presented in Table III-2 above, the EPA chose to use its independent analysis of the Korevaar et al., (2016) data (comprising of 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. There are three reasons for this selection: 1) there is sufficient quantitative data to derive a health impact function for the sensitive population of interest; 2) the analysis adjusts for an appropriate set of confounders, and 3) the neurodevelopmental endpoint – intelligence quotient (IQ) – is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below). The other studies presented in Table III-2 do not provide one or more of these features (USEPA, 2018b).

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The five identified papers evaluated a variety of endpoints with Korevaar et al., (2016) evaluating IQ, Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) using the Bayley Scale to evaluate PDI and MDI, Finken, van Eijsden, Loomans, Vrijkotte, and Rotteveel (2013) evaluating the SD of reaction time, and Endendijk, Wijnen, Pop, and van Baar (2017) evaluating anxiety/depression scores using the Child Behavioral Check List (CBCL). The SD of reaction time from Finken et al., (2013) was not well-received by the peer reviewers (External Peer Review for U.S. EPA, 2018) because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al., (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al., (2017) nor the Finken et al., (2013) analyses had functions for the sensitive life stage (i.e., their analyses were based on the full range of fT4 levels and did not concentrate on the impacts of low-end fT4 levels). For these reasons, the Endendijk et al., (2017) and Finken et al., (2013) papers were not selected for further evaluation.

The Korevaar et al., (2016) original and independent analyses are preferable compared to the Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) studies because neither function derived from the Pop et al., studies was adjusted for confounders. Additionally, both Pop et al., papers have an N < 50 compared to the Korevaar et al., analyses, which have an N of greater than 3,600.[8]

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[8] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609 due to the exclusion of subjects with imputed values for maternal fT4.

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Although the original Korevaar et al., (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al., (2016) EPA reanalysis was chosen over the original analysis because it included modifications to the analysis at the suggestion of the peer review panel. The revised analysis controls for a more parsimonious set of confounders (e.g., previously included variables such as infant gender, maternal parity, birthweight, mother's body mass index (BMI), and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al., (2016) model because of the feedback received during the peer review of the MCLG Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

> *Korevaar et al., [2016] controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values* (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

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The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al., (2016) data, and making decisions about data quality and influential data points in the analysis. That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values. Subsequently, the EPA selected the Korevaar et al., (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ [9].

As indicated above, the EPA has utilized a health protective approach to this analysis consistent with the SDWA definition of the MCLG. The peer reviewers commented that this approach was fit-for-purpose. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. As explained earlier, the results of the EPA's dose-response literature review identified

[9] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the MCLG Approaches Report.

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31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior, and other outcomes such as autism. Among these studies, only 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al., (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when

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assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al., (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek et al., 2017; Roman et al., 2013; Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al., (2011) and Gyllenberg et al., (2016). Although Endendijk et al., (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al., (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al., (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic

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mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al., (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking.

Not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. Therefore, the EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data. In an attempt to minimize uncertainty, the EPA reanalyzed the data collected by Korevaar et al., (2016) using a spline function that estimates a coefficient specifically for the low range of the fT4 data.

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There are a variety of neurodevelopmental endpoints used to examine behavior and cognition in children (e.g., intelligence quotient (IQ), motor skills, vocabulary and language development, stimulus responsiveness, etc.). The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al., (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. As such, in the derivation of the MCLG, IQ is a surrogate for a suite of potential neurodevelopmental effects that might occur to the offspring of hypothyroxinemic and iodine deficient mothers.

There are several different tests that are widely used to measure IQ in children, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated

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high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

Associations have been found between IQ scores and both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al., (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). Research suggests that children's rearing environment, including parental education, while growing up may increase IQ scores in adolescence by several points (e.g., Kendler et al., 2015).

IQ scores have been used to help diagnose disorders such as intellectual disability and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) IQ scores are used in an individual's comprehensive assessment to determine intellectual disability, which pairs standardized testing of intelligence with a clinical assessment of adaptive functioning. Intellectual disability is considered for individuals with an IQ score of about 70 or below (American Psychiatric Association, 2013).

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 percent extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when

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using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint. Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, USEPA, 2012).

For the specific context of setting an MCLG for perchlorate, the EPA made a policy decision to evaluate the level of perchlorate in water associated with a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points). The EPA selected IQ as a surrogate for neurodevelopmental effects based upon its evaluation of the epidemiologic literature describe above. The need to utilize the best available peer reviewed data to inform scientific assumptions and policy choices to meet the statutory requirements associated with developing an MCLG under the SDWA highlights the challenges associated with regulating chemicals for which potential effects are indirect, and scientific data do not address all uncertainties. The Agency must make a policy decision informed by science, consistent with statutory requirements even in situations where the data do not provide clear choices. To develop the proposed MCLG for perchlorate, the EPA made a policy decision to use a 2 IQ point decrement in the population-distribution of IQ for the sensitive population. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants for which there is concern about potential thyroid effects, either under the SDWA or other statutory frameworks.

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Applying these response rates to the results from the reanalysis of Korevaar et al., (2016), results in a POD dose of 3.1 μg/kg/day for a 1 point decrease in the sensitive population's IQ, a POD dose of 6.7 μg/kg/day for a 2 point decrease in the sensitive population's IQ, and a POD dose of 10.8 μg/kg/day for a 3 point decrease in the sensitive population's IQ. These PODs associated with a 1, 2, or 3 point decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the POD is designed to provide an adequate margin of safety for the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 μg/day and a TSH feedback loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the methodological reasons described previously, the EPA believes that the selection of these parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive population and allows for an adequate margin of safety.

I. Translate PODs to RfDs

When deriving an RfD the EPA evaluates whether to apply uncertainty/variability factors to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002). As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a no-observed-adverse-effect-level (NOAEL), and an incomplete database. The factors are intended to account for: 1) variation in susceptibility among the

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members of the human population (i.e., inter-individual or intraspecies variability); 2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); 3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); 4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and 5) uncertainty associated with extrapolation when the database is incomplete. (U.S. EPA, 2011b) The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., uncertainty factor (UF) for within-human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. The approach taken to derive the RfD attempts to address variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and

[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the MCLG Approaches Report.

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the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.

Further, as discussed in section III.C. of this notice the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. In addition, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is potentially because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et al., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the fetal thyroid begins secreting thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels available to the fetus. Given that the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that

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may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. Therefore, as described above, the EPA selected an intraspecies UF of 3 to account for the uncertainties in modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children.

The EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. As noted above, the Agency has opted to apply a UF of 3 to the POD, which adds an adequate margin of safety to the MCLG derivation. Section 4.4.5.3 (p 4-42) of *A Review of the RfD & RfC Processes* recommends reducing the intraspecies UF from a default of 10 "only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)" (p. xviii, USEPA, 2002).The EPA selected a UF of 3 instead of the full 10 because the modeled groups within the population that are identified as likely to be at greater risk

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

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to perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother) and has selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake).

Below we list the other uncertainty factors added and the justification.

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.
- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.
- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.
- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an

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incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).

- The product of all the uncertainty factors (UF_H) is 3 (3 x 1 x 1 x 1 x 1).

Below we generate RfD's for each of the points of departure.

Using the POD of 6.7 µg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.2\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 µg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.0\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

J. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 µg/kg/day for a 1 percent decrease in IQ, 2.23 µg/kg/day for a 2 percent decrease in IQ, or 3.6 µg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution of drinking water to overall perchlorate exposure.

To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate specific to women of childbearing age (i.e., non-pregnant, non-lactating, 15–44 years of age (0.032 L/kg/day). This decision is consistent with the analysis used in deriving an RSC, which was performed using food consumption information for a population of women of childbearing age from NHANES. The 90th percentile is chosen to account for variability in drinking water ingestion rates, but also adds another layer of health protection for 90% of women (Table III-3).

The EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable. The use of the drinking water intake for 15-44 year old women is consistent with the analysis used in deriving an RSC_w (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of

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ages used to define women of childbearing age in developing the BBDR model. However, the EPA's Exposure Factors Handbook (USEPA, 2011c) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis.

Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

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To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2019c). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in about 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (μg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The details of these assumptions are explained on page 5-5 of the Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (USEPA 2019c). Specifically, the EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the 20 samples included in the TDS data. In order to estimate the 95th percentile from the 20 samples, the EPA used the second-highest test result for each food to represent the 95th percentile concentration. While simple, this

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method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine [ADDIN EN.CITE <EndNote><Cite><Author>Carriquiry</Author><Year>2016</Year><RecNum>2008</RecNum><DisplayText>(Carriquiry et al., 2016)</DisplayText><record><rec-number>2008</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039524">2008</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carriquiry, A. L. </author><author>Spungen, J. H.</author><author>Murphy, S. P.</author><author>Pehrsson, P. R.</author><author>Dwyer, J. T.</author><author>Juan, W.</author><author>Wirtz, M. S. </author></authors></contributors><titles><title>Variation in the iodine concentrations of foods: considerations for dietary assessment</title><secondary-title>The American Journal of Clinical Nutrition</secondary-title></titles><periodical><full-title>The American Journal of Clinical Nutrition</full-title></periodical><pages>877S–887S</pages><volume>104</volume><number>Suppl 3</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. The aforementioned method for identifying the 95th percentile concentration of perchlorate from food was selected over other, more “statistically based” methods for estimating percentiles as it avoids the need to assume a distributional shape for the samples. The EPA determined that it was more reliable to assume the empirically derived distribution as the basis for selecting the 95th percentile (i.e., assuming the distribution was equal to the distribution of samples collected in the TDS), as opposed to forcing a distributional shape, such as normal or log-normal, onto the data

that may not necessarily be appropriate. With the chosen method, we can at least be sure that the distributional shape is appropriate for the data at hand, whereas by choosing the alternative that assumes a distributional shape, in many instances we would not even be certain of that. The EPA used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 μg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile perchlorate food concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

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Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

The EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III-5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using the EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.0	56%	0.032	18
2.2	80%	0.032	56
3.6	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss, 2-point IQ loss, or a 3-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

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$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the NPDWR. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 µg/L based on the rationale and methodology described in Section III above. The derivation of the proposed MCLG uses a point of departure based upon a two percent decrease in IQ for offspring of hypothyroxinemic women of child bearing age have with low iodine intake. The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the subpopulation of interest.

As described in Section III, the EPA has selected model parameters and other factors for the derivation of the MCLG that are health protective, including the focus on the most sensitive life stage. The EPA believes that the selection of the combination of protective parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive subpopulation and allows for an adequate margin of safety. The EPA also acknowledges the uncertainties in the derivation of the proposed (and alternative) MCLGs. The EPA acknowledges in particular the challenge associated with selecting the decrement of IQ that

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represents an adverse effect at the population level and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement given the absence of robust human epidemiological data directly linking perchlorate exposure to IQ decrements. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2019b). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018c). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

Because the EPA is taking comment on alternative MCLG values of 18 µg/L and 90 µg/L the Agency evaluated the feasibility of setting an MCL at these levels. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this

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level under field conditions (USEPA 2018a, 2019b). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed

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science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA Section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The UCMR 1 is the primary source of occurrence data the EPA relied on to estimate the number of water systems (and associated population) expected to be exposed at levels of perchlorate which could potentially exceed the proposed and alternative MCL levels. Since UCMR 1 data was first used to inform the Agency actions on the 2008 preliminary regulatory determination and the 2011 final regulatory determination, the Agency has modified its analysis of the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions at some States that have enacted perchlorate regulations since the UCMR 1 data was collected. Despite these updates, the EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants

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(USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to the EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 μg/L for perchlorate in the UCMR.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

In September of 2012, the EPA received a "Request for Correction" letter from the United States Chamber of Commerce regarding information and data (i.e., the occurrence of perchlorate in drinking water) used by the EPA in its 2011 determination to regulate perchlorate. The U.S. Chamber of Commerce letter stated that the EPA relied upon: 1) data that did not comply with data quality guidelines and 2) data that was not representative of current conditions.

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In response[12] to the U.S. Chamber of Commerce, the EPA conducted a detailed assessment of the source water sample detections and determined that it was most appropriate to exclude the source water sample detections from the UCMR 1 perchlorate data set when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 perchlorate data set. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 perchlorate data set. As a result of the assessment, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the entry point to the distribution system. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections from 149 PWSs.

Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

In response to the U.S. Chamber of Commerce request, the EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two states. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION

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[12] See the EPA response letter at https://www.epa.gov/sites/production/files/2017-08/documents/12004-response_0.pdf

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{"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states are now required to

keep perchlorate levels in drinking water below their state limits, which are lower than the proposed MCL and alternative MCLs. Therefore, the UCMR 1 sampling results from systems in these states do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. The notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

To update the occurrence data for systems sampled during UCMR 1 from the States of California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

Out of the 540 detections previously described the EPA updated data for 321 detections (320 from California systems and 1 from a Massachusetts system). The convention used by the EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported compliance monitoring data, if more than one

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data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were the EPA could not find updated entry point data, then the original data from UCMR 1 for such entry point was kept.

Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 µg/L	15	525	540
Sample measurements > 18 µg/L	1	16	17
Sample measurements > 56 µg/L	0	2	2
Sample measurements > 90 µg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 µg/L	8	328	336
Entry points at which measurements > 18 µg/L	1	16	17
Entry points at which measurements > 56 µg/L	0	2	2
Entry points at which measurements > 90 µg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 µg/L	8	141	149
Systems at which measurements > 18 µg/L	1	14	15
Systems at which measurements > 56 µg/L	0	2	2
Systems at which measurements > 90 µg/L	0	1	1

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UAoGFPZv","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The total row counts and counts of measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population

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is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements > 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements > 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements > 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ChxDKgDr","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting

level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCLs. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"adhRbcXq","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

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Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

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{"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In summary, the perchlorate occurrence information suggests that at an MCL of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. One of these two systems would exceed the alternative MCL of 90 µg/L. In addition, at an MCL of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is ''feasible'', the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, the SDWA directs the EPA to determine that it is economically and technologically feasible to

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ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain ''criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels.'' (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report (USEPA, 2019b).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of sample analysis and data reporting. All of the proposed EPA analytical methods provide

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performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

The EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework set out in 40 CFR 141 Subpart C (Standardized Monitoring Framework). Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. The EPA is proposing that consistent with the standardized monitoring framework water systems would be initially required to monitor quarterly for perchlorate. The EPA is also proposing that based upon the monitoring results States would be able to reduce the monitoring frequency to annually, once every three years or once every nine years if the State concludes that the system is reliably and consistently below the MCL. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point in the next quarter after the violation occurred (40 CFR 141.23(c)(7)). The state may allow the system to return to the reduced monitoring frequency when the state determines that the system is reliably and consistently below the MCL. However, the state cannot make a determination that the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples below the MCL have been collected (40 CFR

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141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the state (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under this proposal, water systems may apply to the state, and states may grant, a 9-year monitoring waiver for perchlorate if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A state may grant a waiver for surface water systems after three rounds of annual monitoring with results less than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

Under this proposal, violations of the perchlorate MCL would be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the perchlorate MCL would be determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than

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10,000 persons must collect 4 quarterly samples for perchlorate during the second compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the Standardized Monitoring Framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the third compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the Standardized Monitoring Framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered perchlorate data collected after January 1, 2020, to satisfy the initial monitoring requirements. To satisfy initial perchlorate monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for CWSs serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for NTNCWs and for CWSs serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

A community water system must prepare and deliver to its customers an annual Consumer Confidence Report (CCR) in accordance with requirements in 40 CFR 141 Subpart O. A CCR provides customers with information about their local drinking water quality as well as information regarding the water system compliance with drinking water regulations. Under this proposal CWSs would be required to report perchlorate information in their CCR.

B. What are the Public Notification Requirements?

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All public water systems must give the public notice for all violations of NPDWRs and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, per 40 CFR 141.202(b)(1), notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation under this proposal.

X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by states to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in states issuing small system variances under Section 1412(e) of the SDWA.

The Agency solicits public comment on the choice of available treatment technologies discussed in this section.

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A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal

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efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"s9dVZckb","properties":{"formattedCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","plainCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","noteIndex":0},"citationItems":[{"id":1048,"uris":["http://zotero.org/groups/945096/items/KIPNEQUM"],"uri":["http://zotero.org/groups/945096/items/KIPNEQUM"],"itemData":{"id":1048,"type":"paper-conference","title":"Castaic Lake Water Agency Operating Experience with Lead-Lag Anion Exchange for Perchlorate Removal","container-title":"Proceedings of the American Water Works Association Water Quality Technology Conference","event":"Water Quality Technology Conference","author":[{"family":"Drago","given":"J.A."},{"family":"Leserman","given":"J.R."}],"issued":{"date-parts":[["2011",11]]}}},{"id":1154,"uris":["http://zotero.org/groups/945096/items/2DBS6UYD"],"uri":["http://zotero.org/groups/945096/items/2DBS6UYD"],"itemData":{"id":1154,"type":"article","title":"News: Ion=Exchange System Removes Perchlorate","publisher":"Membrane Technology","author":[{"literal":"Membrane Technology"}],"issued":{"date-parts":[["2006",4]]}}},{"id":1125,"uris":["http://zotero.org/groups/945096/items/6WYYWFY2"],"uri":["http://zotero.org/groups/945096/items/6WYYWFY2"],"itemData":{"id":1125,"type":"re

port","title":"Case Study: Municipality in the State of Massachusetts","author":[{"literal":"Siemens Water Technologies"}],"issued":{"date-parts":[["2009"]]}}},{"id":1118,"uris":["http://zotero.org/groups/945096/items/5PV8GPIA"],"uri":["http://zotero.org/groups/945096/items/5PV8GPIA"],"itemData":{"id":1118,"type":"article","title":"Technical/Regulatory Guidance: Remediation Technologies for Perchlorate Contamination in Water and Soil","URL":"http://www.eosremediation.com/download/Perchlorate/ITRC%20PERC-2.pdf","author":[{"literal":"The Interstate Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, i.e., the contaminant "breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on

studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cxQjBTo8","properties":{"formattedCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","plainCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}

],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed (i.e., operated on a 'throw-away' basis). This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"I0SaZZiL","properties":{"formattedCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/item

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s/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"dat

e-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Ion exchange can increase the corrosivity of treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dcLyBjzj","properties":{"formattedCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","plainCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":1079,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":1079,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1078,"uris":["http://zotero.org/groups/945096/items/BNWD5VQP"],"uri":["http://zotero.org/groups/945096/items/BNWD5VQP"],"itemData":{"id":1078,"type":"article-journal","title":"Rotation ion-exchange system removes perchlorate","page":"454A-455A","volume":"32","journalAbbreviation":"Environ. Sci. Technol.","author":[{"family":"Betts","given":"K.S."}],"issued":{"date-parts":[["1998"]]}}},{"id":1208,"uris":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"uri":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"itemData":{"id":1208,"type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}] because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench-scale tests and full-scale treatment plant studies [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CnYkqct9","properties":{"formattedCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1019,"uris":["http://zotero.org/groups/945096/items/E5WRR4HD"],"uri":["http://zotero.org/groups/945096/items/E5WRR4HD"],"itemData":{"id":1019,"type":"article-journal","title":"Evaluation of electron donors for biological perchlorate removal highlights the importance of diverse perchlorate-reducing populations","container-title":"Environmental Science: Water Research & Technology","page":"1049-1063","volume":"2","author":[{"family":"Kotlarz","given":"N."},{"family":"Upadhyaya","given":"G."},{"family":"Togna","given":"P."},{"family":"Raskin","given":"L."}],"issued":{"date-

parts":[["2016"]]}}},{"id":1106,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1106,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR, respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 μg/L ClO4–. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 μg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-parts":[["2015",12,1]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"

],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}},{"id":1093,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1093,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and

Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nKwIqjde","properties":{"formattedCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/

BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ISPg08cl","properties":{"formattedCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","plainCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","noteIndex":0},"citationItems":[{"id":1047,"uris":["http://zotero.org/groups/945096/items/X3WWHCXS"],"uri":["http://zotero.org/groups/945096/items/X3WWHCXS"],"itemData":{"id":1047,"type":"speech","title":"The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher-place":"U.S. Environmental Protection Agency,

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Office of Research and Development, National Risk Management Research Laboratory","event-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1046,"uris":["http://zotero.org/groups/945096/items/IIXUW45F"],"uri":["http://zotero.org/groups/945096/items/IIXUW45F"],"itemData":{"id":1046,"type":"article","title":"Supporting data for presentation: The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1045,"uris":["http://zotero.org/groups/945096/items/FLVLSXCS"],"uri":["http://zotero.org/groups/945096/items/FLVLSXCS"],"itemData":{"id":1045,"type":"speech","title":"The Impact of Temperature on Anaerobic Biological Perchlorate Treatment","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dugan","given":"N.R."},{"family":"Williams","given":"D.J."},{"family":"Meyer","given":"M."},{"family":"Schneider","given":"R.R."},{"family":"Speth","given":"T.F."},{"family":"Metz","given":"D.H."}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in

bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"NDoHjLOr","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"

report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"f4qlOob5","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","noteIndex":0},"citationItems":[{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security

Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ySKwU3Em","properties":{"formattedCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1051,"uris":["http://zotero.org/groups/945096/items/Z7PC3BME"],"uri":["http://zotero.org/groups/945096/items/Z7PC3BME"],"itemData":{"id":1051,"type":"speech","title":"Full-Scale Biological Denitrification Plants in Germany, Austria and Poland","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dordelmann","given":"O."}],"issued":{"date-parts":[["2009",11]]}}},{"id":1026,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1026,"type":"rep

ort","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litch

field","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"edXX3GgQ","properties":{"formattedCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, &

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Her, 2005)","plainCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":985,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-parts":[["1998"]]}}},{"id":986,"uris":["http://zotero.org/groups/945096/items/YHEV76YW"],"uri":["http://zotero.org/groups/945096/items/YHEV76YW"],"itemData":{"id":986,"type":"paper-conference","title":"Perchlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher-place":"Phoenix, AZ","event":"American Water Works Association Membrane Technology Conference","event-place":"Phoenix, AZ","author":[{"family":"Nam","given":"S."},{"family":"Kim","given":"S."},{"family":"Choi","given":"H."},{"family":"Yoon","given":""},{"family":"Silverstein","given":"J."},{"family":"Amy","given":"G."}],"issued":{"date-parts":[["2005"]]}}},{"id":992,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":992,"type":"article-

journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":991,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water.

Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in [REF _Ref529958951 \h]. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"J9AlL73G","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table X-[SEQ Table * ARABIC \s 1]: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, the EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

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The SSCT listed in [REF _Ref529958951 \h] include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 μg/L to a target level of 4 μg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LHgBHn5b","properties":{"formattedCitation":"(USEPA, 1998)","plainCitation":"(USEPA,

1998)","noteIndex":0},"citationItems":[{"id":1215,"uris":["http://zotero.org/groups/945096/items/399QNBY4"],"uri":["http://zotero.org/groups/945096/items/399QNBY4"],"itemData":{"id":1215,"type":"article","title":"Variance Technology Findings for Contaminants Regulated Before 1996","publisher":"EPA 815–R– 98–003. September","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of median household income. [REF _Ref529959037 \h] shows the expenditure margins derived for the analysis. These margins show the cap on affordable incremental annual expenditures.

Table X-[SEQ Table * ARABIC \s 1]: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2scXqyv0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"x096Tc8Y","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1225,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1225,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Rg9m81J","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018b)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018b)","noteIndex":0},"citationItems":[{"id":1226,"uris":["http://zotero.org/groups/945096/items/GTI7H6YK"],"uri":["http://zotero.org/groups/945096/items/GTI7H6YK"],"itemData":{"id":1226,"type":"article","title":"CPI--All Urban Consumers (all items), for areas under 50,000 persons","author":[{"family":"Bureau of Labor Statistics (BLS)","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
b. Affordability threshold equals 2.5 percent of MHI.
c. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fS2Ibu6t","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":163,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":163,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[REF _Ref529959069 \h] shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z6GYvRh1","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance

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Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"18aKvRLD","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":147,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":147,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-[SEQ Table * ARABIC \s 1]: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8y1WSJT4","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.
a. For perchlorate, the EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA Sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

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40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance

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of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant. However, the perchlorate MCL could result in a greater frequency of reporting by certain states. See discussion of Paperwork Reduction Act compliance in Section XVI for more information.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);

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- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);
- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If the EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the

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monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B below summarizes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section C below summarizes this method used to estimate these benefits.

Section D below provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a), which is available in the docket for the proposed rule. Section XIII summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

Some costs associated with an NPDWR are incurred by all CWS and NTNCWS (e.g. monitoring and reporting) while others are only incurred by systems with perchlorate levels exceeding the MCL. The EPA estimated costs for CWS and NTNCWS to monitor and report perchlorate levels and also estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment because it is the most cost-effective treatment option and easy to operate on a 'throw-away' basis. If site-specific

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nontreatment options are available and lower cost, then this assumption might overstate costs. The EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring, report results, and apply for waivers. For the purpose of these estimates, the EPA assumed that both small and large systems would require the same amount of time to read the rule, apply for a waiver, and collect a water sample but that it would take large systems twice as long to provide initial training to their staff. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.
1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

Systems will incur monitoring costs over the analysis period. The EPA estimated monitoring frequency based on the proposed initial monitoring requirements, the standard monitoring framework requirements for inorganic contaminants, and the proposed

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implementation schedule. The estimated number of monitoring samples over the analysis period shown in Table XII-2 reflect the following phases:

1. Initial monitoring; four quarterly samples at every CWS and NTNCWS entry point.

2. Preliminary regular monitoring before waiver application: three regular monitoring samples for every CWS and NTNCWS entry point (collected annually at surface water system entry points and triennially at ground water system entry points).

3. Long-term monitoring at either (a) regular monitoring frequency for entry points at systems not granted waivers (60% of surface water system and 10% of ground water systems), or (b) reduced monitoring frequency for entry points at systems receiving waivers from primacy agencies (40% of surface water systems and 90% of ground water systems), which is one sample during every nine-year compliance monitoring cycle.

Table XII-2: Estimates of Compliance Monitoring Samples by Phase and System Type, Size, and Source Water

Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
1. Initial monitoring (4 quarterly samples in one year)	All CWS and NTNCWS	92,656	370,624
2. Preliminary regular monitoring (3 annual entry point samples for surface water systems and 3 triennial entry point samples for ground water systems)	All CWS and NTNCWS	92,654	277,962
3a. Long-term monitoring, no waiver (annual entry point samples)	60% of large surface water CWS	3,324	86,424
	60% of small surface water CWS and all surface water NTNCWS	6,064	139,472
3a. Long-term monitoring, no waiver (triennial entry point samples)	10% of large ground water CWS	680	4,080
	10% of small ground water CWS and all ground water NTNCWS	7,021	35,105
3b. Long-term monitoring, waiver (1 sample every 9 years)	40% of large surface water CWS	2,216	4,432
	40% of small surface water CWS and all surface water NTNCWS	4,043	8,086

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Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
3b. Long-term monitoring, waiver (1 sample every 9 years)	90% of large ground water CWS	6,117	12,234
	90% of small ground water CWS and all ground water NTNCWS	63,189	63,189

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780).

1. The EPA estimated a total of 92,656 entry points based on the total number of potentially affected systems in SDWIS/FED and the average number of entry points per system in the UCMR 1 data by size category and source water. The initial monitoring phase includes all entry points. The EPA assumed that the two entry points with MCL exceedances at the proposed MCL of 56 µg/L would continue to take quarterly samples for the duration of the analysis period, for a total of 232 samples. Thus, they are excluded from the estimates for the subsequent phases of regular and long-term monitoring. Primacy agencies may, however, allow monitoring to return to a regular schedule if treatment process operation can reliably and consistently reduce perchlorate below the MCL.

2. For Phase 3, the estimate of aggregate samples is the product of the number of entry points and the frequency of sampling during the remaining years of the analysis period. For example, large surface water CWS without a waiver conduct long-term annual monitoring for 26 years because they complete preliminary regular monitoring in year 9. In contrast, large ground water CWS without a waiver begin long-term triennial monitoring in year 16 because their preliminary regular monitoring phase lasts for 9 years (3 triennial samples) instead of 3 years (3 annual samples). The estimates also reflect schedule differences by size because large CWS begin monitoring schedules three years earlier than small CWS and all NTNCWS.

To estimate costs to CWSs and NTNCWSs associated with time spent on compliance monitoring and other administrative costs, the EPA generally uses the labor rate[13] for full-time treatment plant operators in CWSs from USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5g8IJ6Eh","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/FHCVSMRC"],"uri":["http://zotero.org/groups/945096/items/FHCVSMRC"],"itemData":{"id":992,"type":"article","title":"Labor Cost for National Drinking Water Rules","author":[{"family":"USEPA","given":""}],"issued":{"date-

[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

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parts":[["2011"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of system entry points that exceed the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[14]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and nontreatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g.,

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[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c) contains more complete discussion of the WBS models and the cost estimating approach.

105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, the EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 μg/L the blending target would be 45 μg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost

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curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and Agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-3 summarizes the labor hour assumptions for these activities. The EPA requests comments on these assumptions.

Table XII-3: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)

1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.

2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental

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Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"C1A8zUkj","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","plainCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"uri":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"itemData":{"id":984,"type":"webpage","title":"Employer Cost for Employee Compensation -- September 2016","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2016"]]}},"label":"book","suffix":"Table 3"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], for a fully loaded hourly wage rate for States of $50.67. The EPA requests comments on these labor rate assumptions.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while

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systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mnzEXxZK","properties":{"formattedCitation":"(USEPA, 2008b)","plainCitation":"(USEPA, 2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":998,"uris":["http://zotero.org/groups/945096/items/QSXYHBID"],"uri":["http://zotero.org/groups/945096/items/QSXYHBID"],"itemData":{"id":998,"type":"article","title":"Draft Information Collection Request for the Disinfectants/Disinfection Byproducts, Chemical, and Radionuclides Rule","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2008",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a

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full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[15]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Q6RKolIZ","properties":{"formattedCitation":"(U.S. Census Bureau, 2017b)","plainCitation":"(U.S. Census Bureau, 2017b)","noteIndex":0},"citationItems":[{"id":1000,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":1000,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S.

[15] For systems with monitoring costs only, household-level costs will be negligible.

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Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA divided the total annual system-level costs by the number of households served by the system.

C. Method for Estimating Benefits

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children

that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rCNbGglo","properties":{"formattedCitation":"(U.S. Census Bureau, 2017a)","plainCitation":"(U.S. Census Bureau, 2017a)","noteIndex":0},"citationItems":[{"id":189,"uris":["http://zotero.org/groups/945096/items/ZM7S6H44"],"uri":["http://zotero.org/groups/945096/items/ZM7S6H44"],"itemData":{"id":189,"type":"article","title":"Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016.","URL":"https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html#ds","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7XfZyKhY","properties":{"formattedCitation":"(Martin, Hamilton, & Osterman, 2017)","plainCitation":"(Martin, Hamilton, & Osterman, 2017)","noteIndex":0},"citationItems":[{"id":186,"uris":["http://zotero.org/groups/945096/items/MY6LPDKD"],"uri":["http://zotero.org/groups/945096/items/MY6LPDKD"],"itemData":{"id":1

86,"type":"article","title":"Births in the United States, 2016. NCHS Data Brief No. 287","URL":"https://www.cdc.gov/nchs/data/databriefs/db287.pdf","author":[{"family":"Martin","given":"J.A."},{"family":"Hamilton","given":"B.E."},{"family":"Osterman","given":"M.J.K"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 µg/L and alternative MCLs of 18 µg/L and 90 µg/L. The first step relates changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake. For the BBDR simulations, the EPA used the 90th percentile ingestion rate to be consistent with the MCLG modeling approach, which may overstate the exposure in the simulation.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"iqyVRL6z","properties":{"formattedCitation":"(Korevaar et al., 2016)","plainCitation":"(Korevaar et al., 2016)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemD

ata":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including

concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I

M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-4 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

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Table XII-4: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2019a).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants that target the thyroid, such as nitrate, as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XIII provides additional discussion of uncertainties in this analysis.

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D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 µg/L, Table XII-5 summarizes the total estimated cost of the proposed rule to water systems and primacy agencies, and Table XII-6 summarizes the estimated per-household cost for the system incurring treatment costs[16]. Table XII-7 summarizes the estimated benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

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Table XII-5: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

Source: [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-6: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA,

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uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health

Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water

Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-

parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table XII-7: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

For the alternative MCL of 18 µg/L, Table XII-8 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-9 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-10 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

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Table XII-8: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H6Rcd4Hf","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Detail may not sum to total because of independent rounding.

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.

2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-9: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"uu13kmuC","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

Table XII-10: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EN9pibZj","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-11 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-12 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-13

summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

Table XII-11: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-12: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 µg/L because treatment costs to meet an MCL of 90 µg/L are lower than the costs to meet an MCL of 56 µg/L.

Table XII-13: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Table XII-14 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between an MCL of 56 µg/L and an MCL of 18 µg/L and between an MCL of 90 µg/L and 56 µg/L.

Section 1412(b)(4)(C) of the SDWA requires that when proposing a national primary drinking water regulation, "the Administrator shall publish a determination as to whether the benefits of the maximum contaminant level justify, or do not justify, the costs." The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative

cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 µg/L using the best available science and data, the EPA Administrator has determined based upon the available information that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs.

Under these circumstances, Section 1412(b)(6)(A) of the SDWA provides, with exceptions not relevant here, that "the Administrator *may*, after notice and opportunity for public comment promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits." The EPA has evaluated the benefits and costs of alternative MCL values of 18 µg/L and 90 µg/L. However, based upon the available information the Administrator also finds that the benefits of an NPDWR at the alternative MCL values would not justify the resulting rule costs. The alternative MCLs would not increase net benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar. Consistent with the discretion afforded the Agency by SDWA Section 1412(b)(6)(A) to decide whether or not to adjust an MCL to a level where the benefits justify the costs, the EPA is however proposing, and may finalize, the MCL of 56 µg/L notwithstanding the Agency's determination that benefits would not justify the costs.

Table XII-14: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05

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Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E0mmmXDK","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Detail may not sum to total because of independent rounding.
1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA has presented an extensive discussion of the uncertainties in the key analyses informing this proposal in the uncertainty section of the MCLG Approaches Report and the uncertainties section of the Economic Analysis document (*USEPA, 2018b; USEPA, 2019a)*. A summarized description of these uncertainties are presented below.

A. Uncertainty in the MCLG Derivation

Each input into the analysis to inform the MCLG is a decision point associated with uncertainty. There is uncertainty in different aspects of the BBDR model, ranging from structural and functional relationships to specific parameter values for early pregnancy. There are very few data available to calibrate the pharmacokinetic aspects of the model, particularly at the life stage of interest. Also, the BBDR model does not explicitly consider the effect of the presence of other

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goitrogens (e.g. thiocyanate, nitrate) or effects of thyroid disease states. Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. Additional uncertainty is introduced by linking the BBDR model estimates of maternal fT4 to altered neurodevelopment in offspring. None of the studies used to evaluate potential adverse neurodevelopmental outcomes in offspring born to hypothyroxinemic mothers was performed in the U.S. None of the studies measured perchlorate exposure. Not all the studies measured iodide levels in the study populations. The state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. There are numerous indices used to assess neurodevelopmental impacts and there is some uncertainty regarding the selection of IQ as the critical endpoint for setting the MCLG.

A recently published paper evaluating the EPA's BBDR model and MCLG Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al., 2019).

B. Uncertainty in the Economic Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2019a). Table XIII-1 provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

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Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect[1]
Baseline Occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water).	± (benefits and costs will change in the same direction)
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 µg/L or 90 µg/L and that one small system would exceed 18 µg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than the MCLs that are not captured in the national extrapolation results.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum.	± (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4.	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The EPA used a 90th percentile water intake rate to derive the MCLG and the dose-response equations for the benefits analysis. This approach results in a protective MCLG value, but may overstate intake for the benefits analysis[2].	+ (benefits only)
The IQ valuation uses estimates that the EPA derived using the same approach as Salkever (1995). Results from other IQ valuation studies might result in higher or lower benefit estimates.	± (benefits only)
The benefits analysis is based on a single health endpoint and the value of the endpoint is based solely on lost earnings.	− (benefits only)

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Description	Potential effect[1]
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)
The EPA assumed that all entry points requiring treatment would implement ion exchange, which may overestimate costs if non-treatment is an option for one or more entry points or underestimate costs if site-specific conditions result in higher costs at one or more entry points.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	− (costs only)
The EPA assumed that 90% of ground water systems and 40% of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "−" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.
2. The EPA did not include a perchlorate dietary dose in the benefits analysis, which would be unchanged between baseline and proposed MCL scenarios if many areas do not irrigate with drinking water. For people who obtain a significant portion of their fruit, vegetables, and milk from areas irrigated with the water from the same sources as the drinking water, we would expect their exposure may drop with the reduction of perchlorate in food products used locally. Because of this and the natural log form of the IQ response function, this approach may slightly understate the avoided IQ decrement estimates.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional

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disorders in childhood (Man et al., 1991; Pop et al., 1999; Pop et al., 2003; Kooistra et al., 2006)" (p. 10, SAB for the U.S. EPA, 2013). The EPA's literature review identified potential relationships between maternal thyroid hormone alterations and the risk of schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include risks associated with effects of thyroid disorders in adults, including cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints are not monetized in this benefits analysis. The assumptions used to account for the previously mentioned variability of the BBDR model inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above may result in an overestimate of the monetized benefits. Because IQ is a surrogate for broad range of potential neurodevelopmental risks, it is unclear whether the analysis as a whole over- or under-estimates the monetized benefits of a reduction of perchlorate in drinking water.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues will be especially helpful to the EPA in developing a final rule. The EPA specifically requests comment on the following topics.

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- The adequacy and uncertainties of the BBDR model developed by the EPA to predict thyroid hormone level changes caused by perchlorate exposure to pregnant women with low iodide intake, including the model and model parameters and assumptions (Section III and Approaches Report).
- The adequacy and uncertainties of the EPA's review and application of the epidemiologic literature to quantify the relationship between thyroid hormone changes in pregnant women and neurodevelopmental effects including the assumptions, the selection of the approach used, and the study used (Section III and Approaches Report).
- The adequacy and uncertainties of the methodology to derive the MCLG including points of departure, assumptions, uncertainty factor, and relative source contribution (Section III and Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water).
- The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.
- The feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.
- The adequacy of the underlying assumptions and analysis of occurrence (Section VI).
- The costs and availability of Treatment Technologies (Section X).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate costs and describe unquantified costs including the estimates of monitoring frequency, likelihood

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of systems receiving a monitoring waiver, the administrative labor rate and the operator labor rate. (Section XII and the Health Risk Reduction Cost Analysis).

- The adequacy of the underlying estimates, assumptions and analysis used to estimate benefits and describe unquantified benefits (Section XII and the Health Risk Reduction Cost Analysis).
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's finding in accordance with Section 1412(b)(4)(C) of the SDWA that the benefits of the proposed 56 µg/L MCL for perchlorate do not justify the costs, and the information that supports that determination as described in Section XII of this notice.
- The Administrator's proposal to, consistent with the discretion afforded him by SDWA Section 1412(b)(6)(A), adopt an MCL of 56 µg/L notwithstanding the Agency's SDWA Section 1412(b)(4)(C) determination that the benefits of the MCL would not justify its costs.
- The Agency's conclusion that no alternative MCL, including the alternative MCL values of 18 µg/L and 90 µg/L discussed above, would "maximize health risk reduction benefits at a cost that is justified by the benefits" and the information and analytical approaches used to arrive at that conclusion. The EPA is especially interested in comments suggesting other approaches to deriving an MCL for which the benefits justify the costs.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on several factors. First, the findings, described in the

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occurrence section (section VI) and in the updated health effects assessment (Section III), suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern[17] and suggest that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate, but the available data indicates that very few would find it at levels of public health concern. Specifically, perchlorate occurrence information suggests that at an MCL of 56 µg/L only 2 systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Even at an MCL of 18 µg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. Only one system would exceed the alternative MCL of 90 µg/L.

The EPA notes that in 2008, the EPA stated in its preliminary regulatory determination that perchlorate did not occur with a frequency and at levels of public health concern in public water systems based upon the health effects and occurrence information available at that time, which indicated that 0.8% of public water system had perchlorate at levels exceeding the HRL of 15 µg/L. The EPA also stated that there was not a meaningful opportunity for a NPDWR to reduce health risks based upon the estimates at that time that 0.9 million people had perchlorate levels above the HRL.

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[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or 90 µg/L, which are the possible levels expected to cause adverse human health effects.

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The EPA further notes that the Agency has previously determined CCL1 and CCL2 contaminants did not occur with frequency at levels of public health concern when the percentage of water systems exceeding the HRL were greater than the frequency of perchlorate occurrence level at the proposed MCL (0.004% of all water systems in the U.S.). For example, in 2003 the EPA determined that aldrin did not occur with a frequency and at levels of public health concern based upon data that showed 0.2% of water systems had aldrin at levels greater than the HRL. The EPA also concluded that there was not a meaningful opportunity for health risk reduction for persons served through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 1 million people (USEPA, 2003). In 2008 the EPA determined that DCPA Mono- and Di-Acid degradates did not occur with a frequency and at levels of public health concern based on data that showed 0.03% of water systems exceeded the HRL. The EPA also included that there was not a meaningful opportunity for health risk reduction through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 100,000 people (USEPA, 2008e).

SDWA Section 1412(b)(1)(A)(iii) states that the determination regarding the meaningful opportunity is "in the sole judgement of the Administrator" and therefore there may be other factors that contribute to this determination for any given contaminant.

If, after consideration of public comment, the EPA withdraws the perchlorate regulatory determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes.

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As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using its SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authorities, as appropriate. The EPA also requests comments on what guidance it could provide the public if the regulatory determination for perchlorate is withdrawn.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a)* is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in the EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act,

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44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The monitoring information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule including adopting the NPDWR into state regulations, providing training to state and PWS employees, updating their monitoring data systems, and reviewing system monitoring data and waiver requests. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) would not begin until after Year 3 due to the proposed effective date of this rule.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to

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comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to the EPA at the public docket established for this rule, which includes the ICR, Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

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The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 μg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 7 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a). Table XII-1 and Table XII-2 show the annual compliance costs of the proposed rule on the small entities by system size for public and private systems, respectively. Based on a comparison of annual costs with annual revenue estimates, the EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2019a).

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Table XII-1: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Public CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$224,248	$88 (0.04%)	$94 (0.04%)
Population served 101-500	$197,315	$88 (0.04%)	$94 (0.05%)
Population served 501-3,300	$202,382	$88 (0.04%)	$94 (0.05%)
Population served 3,301-10,000	$1,092,187	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,16]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Revenues include all sources of revenue including water revenue, non-water revenue, and municipal transfers to water systems.

b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

Table XII-2: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Private CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$139,911	$88 (0.06%)	$94 (0.07%)
Population served 101-500	$351,974	$88 (0.03%)	$94 (0.03%)
Population served 501-3,300	$254,706	$88 (0.03%)	$94 (0.03%)
Population served 3,301-10,000	$951,692	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,16]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Revenues include all sources of revenue including water revenue and non-water revenue.
b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

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F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of Tribal officials early in the process of developing this proposed regulation to permit them to have

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meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a webinar with interested tribes on February 28, 2012, to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012a). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk

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reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2019a) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

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The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. The EPA methods 314.0, 314.1, 314.2, 331.0, and 332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such

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bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking

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Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC, 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (USEPA, 2012; NRC, 2005). On May 29, 2013, the EPA received significant input from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (USEPA, 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking process for perchlorate (USEPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (USEPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (USEPA 2013a).

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Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). The EPA provided information to HHS officials on the draft proposed perchlorate regulation and considered HHS input as part of the interagency review described in section XVII.A.

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List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew R. Wheeler,

Administrator.

ED_005043_00061246-00185

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

   k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

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l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."

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8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."
9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b), 141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

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§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*******	*******	*******	*******
Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM])
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.00002
*******	*******	*******	*******

*****

*****

(c)***

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(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023, and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2026, and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023, and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution

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system may use the monitoring data from the compliance monitoring period that began between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

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(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	**Methodology[13]**	**EPA**	**ASTM[3]**	**SM[4] (18th, 19th ed.)**	**SM[4] (20th ed.)**	**SM Online[22]**	**Other**
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed	314.1					

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	Conductivity Detection Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection Liquid Chromatography Electrospray Ionization Mass Spectrometry Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	314.2 331.0 332.0					
******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

*****

[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods

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for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

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Contaminant	Preservative[1]	Container[2]	Time[3]
*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

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Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L
*******	*******

*****

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

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*****

(b)***

Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000

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persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	**Traditional MCL in mg/L**	**To convert for CCR, multiply by**	**MCL in CCR units**	**MCLG**	**Major sources in drinking water**	**Health effects language**
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						
********	********	********	*******	*******	*******	*******

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Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation
*******				
B. Inorganic Chemicals (IOCs)				
*******				

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14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			
C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

[2] MCL – Maximum contaminant level

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PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14

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*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

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Message

From: Corr, Elizabeth [Corr.Elizabeth@epa.gov]
Sent: 4/15/2019 8:29:04 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: FW: Perchlorate (attachments)
Attachments: REDLINE - EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190415.docx; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190415.docx

Sent to OP (cc'ed to OW colleagues for records and CMS purposes).

From: Corr, Elizabeth
Sent: Monday, April 15, 2019 4:24 PM
To: Nurse, Leanne <Nurse.Leanne@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Perchlorate (attachments)

Hello OP Colleagues,
I am sending the edits from your exchange with Eric Burneson directly to you, per discussion with Christine Ruf.
Feel free to flag me if questions,
Regards,
Elizabeth

Elizabeth Corr
Senior Advisor
Office of Ground Water and Drinking Water
USEPA
Washington DC 20460
(202) 564-3798

From: Hernandez-Quinones, Samuel
Sent: Monday, April 15, 2019 3:19 PM
To: Corr, Elizabeth <Corr.Elizabeth@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Perchlorate

Ms. Corr,

Attached, as requested, are copies of the revised clean and reline versions of the Perchlorate FRN for your transmittal to OP.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water

Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Monday, April 15, 2019 2:49 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Corr, Elizabeth <Corr.Elizabeth@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: FW: Perchlorate

Sam:
Can you make the changes to the document below (The change I suggested to page 14 and the edits to 32 and 97 that were proposed by OP.
Please send a revised and clean version of the FRN to Elizabeth Corr for her to transmit to OW for them to transmit to OP.
No need to redo the memos or other documents.
Thanks
Eric

From: Nickerson, William
Sent: Monday, April 15, 2019 2:37 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Perchlorate

I got the green light on your message below. Thanks for continuing to play ball.

Can you make those edits to the package and resend it to Leanne Nurse in OP? She can then make sure the latest version is that one that is transmitted to OMB.

From: Burneson, Eric
Sent: Monday, April 15, 2019 1:25 PM
To: Nickerson, William <Nickerson.William@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Perchlorate

Bill: We are okay with the suggestions to pages 32 and 97. However we believe that the edit to page 14 suggests a bigger gap in confidence regarding the relationship hypothyroxinemia has with IQ and the other developmental endpoints (note that this is related to but different from the continuous function between thyroid hormone levels (T4) and neurodevelopmental outcomes). We think the following edit is a better characterization of the understanding of the relationship between hypothyroxinemia and these other outcomes:

- "Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to IQ decrements in offspring. There is also limited evidence to suggest an ~~possible~~ association with other adverse neurodevelopmental outcomes

[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development"

Let us know if you would like to discuss this further.
Eric

From: Nickerson, William
Sent: Monday, April 15, 2019 11:04 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Perchlorate

I think this is the key subset of suggested edits

- Page 14 – The description of potential health effects is lacking an important caveat.
  - Original wording: "Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[1], have been linked to IQ decrements in offspring and associations have been found with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development"
  - Suggested wording: "Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to IQ decrements in offspring. There is also limited evidence to suggest a possible association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development"
- I also request the following edits.
  - Page 32 - "After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior, and other outcomes ~~such as schizophrenia~~."
  - Page 97 – "The results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior and other outcomes ~~such as schizophrenia~~."

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[1] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.
[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

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ENVI RONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment

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technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, EPA is requesting comment upon three alternatives: 1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18 µg/L), 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 µg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011 determination to regulate perchlorate in drinking water. Under this alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at [HYPERLINK "http://www.regulations.gov"]. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information

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whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit [HYPERLINK "http://www2.epa.gov/dockets/commenting-epa-dockets"].

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

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F. *Executive Order 13132: Federalism*

G. *Executive Order 13175: Consultation and Coordination with Indian Tribal Governments*

H. *Executive Order 13045: Protection of Children from Environmental Health and Safety Risks*

I. *Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use*

J. *National Technology Transfer and Advancement Act of 1995*

K. *Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations*

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulations (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of 56 µg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 µg/L.

The EPA is proposing a national primary drinking water regulation for perchlorate in accordance with its February 11, 2011 (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is proposing two alternative MCLG/MCL values of 18 µg/L and 90 µg/L respectively. Third, because of the low levels of occurrence of perchlorate at the levels of concern, this action also discusses and requests comment on an alternative action under which EPA would withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems
State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

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Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms, which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate, used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Regulatory History

This section describes the process that led the Agency to propose an NPDWR for perchlorate. The SDWA requires the EPA to make determinations every five years whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify

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priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data and encourage further research on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

Under Section 1412(b)(1)(B)(ii), the EPA must consider the occurrence data collected through the Unregulated Contaminant Monitoring Rule (UCMR). Between 2001 and 2005, the EPA required all large systems serving more than 10,000 people and a representative sample of small systems to monitor for perchlorate and 25 other contaminants under the first UCMR cycle (UCMR 1). Occurrence data generated through UCMR 1 is discussed further below.

To better understand the health effects of perchlorate, the EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate

ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by the NIS, which may lead to decreases in T3 and T4 and increases in TSH [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The NRC recommended, and the EPA adopted, a reference dose (RfD) of 0.7 μg/kg/day. A reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects during a

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

lifetime. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment

Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA, 2008a)","plainCitation":"(USEPA, 2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation

(NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Using this health reference level of 15 µg/L the EPA also published an interim health advisory (HA) for perchlorate. HAs, which are not regulations, contain recommended concentrations of drinking water contaminants at which

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adverse health effects are not anticipated to occur over specific exposure durations. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and the life stage-specific bodyweight and exposure information [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"XzGawKtq","properties":{"formattedCitation":"(USEPA, 2009a)","plainCitation":"(USEPA, 2009a)","noteIndex":0},"citationItems":[{"id":309,"uris":["http://zotero.org/groups/945096/items/ILBCYL66"],"uri":["http://zotero.org/groups/945096/items/ILBCYL66"],"itemData":{"id":309,"type":"report","title":"Inhibition of the Sodium-Iodide Symporter By Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically Based Pharmacokinetic (PBPK) Modeling (Final Report)","collection-title":"EPA/600/R-08/106A","publisher-place":"Washington, D.C.","event-place":"Washington, D.C.","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

After considering comments on the October 2008 and August 2009 notices, the EPA made a final determination in February 2011 to regulate perchlorate in drinking water [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"E1I1fclP","properties":{"formattedCitation":"(USEPA, 2011a)","plainCitation":"(USEPA, 2011a)","noteIndex":0},"citationItems":[{"id":929,"uris":["http://zotero.org/groups/945096/items/4EFIN6HN"],"uri":["http://zotero.org/groups/945096/items/4EFIN6HN"],"itemData":{"id":929,"type":"webpage","title":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","URL":"https://www.federalregister.gov/articles/2011/02/11/2011-2603/drinking-water-regulatory-determination-on-perchlorate","shortTitle":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than May 28, 2019, and finalize a NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The consent decree is available in the docket for today's proposed rule.

III. Health Effects

Perchlorate exposure may adversely affect human health (ATSDR 2008; SAB, 2013; Taylor et al., 2015). Specifically, perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the protein that transports iodide from blood to the thyroid gland (Greer et al., 2002; NRC, 2005; ATSDR; 2008). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

Exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland. A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that

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thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased thyroid stimulating hormone (TSH), the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"eF6zWm7L","properties":{"formattedCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","plainCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","noteIndex":0},"citationItems":[{"id":428,"uris":["http://zotero.org/groups/945096/items/UIANA947"],"uri":["http://zotero.org/groups/945096/items/UIANA947"],"itemData":{"id":428,"type":"bill","title":"Toxicological Profile for Perchlorates","author":[{"family":"ATSDR","given":""}],"issued":{"date-parts":[["2008"]]}}},{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid tormone levels in adolescent and adult men and women living in the United States","container-title":"Environmental Health Perspectives","page":"1865-

1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]}}},{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the national health and nutrition examination survey 2007-8","container-title":"Environmental research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors ...","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID:

23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]}}},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy, including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an

industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L. Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl

","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to IQ decrements in offspring. There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

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[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

The Agency's understanding of the effects of perchlorate on health has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of key thyroid hormones (triiodothyronine (T3) and thyroxine (T4)), and increased thyroid stimulating hormone (TSH). The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency).

Based on NRC's recommendations, the EPA adopted a perchlorate reference dose (RfD) of 0.7 µg/kg/day in 2005 (U.S. EPA, 2005). This value was based on a no observed effect level (NOEL) of 7 µg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

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The EPA derived an HRL of 15 µg/L using the RfD of 0.7 µg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (primarily food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the most sensitive population, fetuses during pregnancy.

On October 10, 2008, the EPA published a preliminary negative regulatory determination for perchlorate and requested public comment on its determination that a NPDWR for perchlorate would not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA estimated that less than 1% of drinking water systems had perchlorate levels above the HRL of 15 µg/L. Therefore, the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In December 2008, the EPA issued an interim health advisory (15 µg/L perchlorate in drinking water) to provide guidance to State and local officials in their efforts to address perchlorate contamination in drinking water (U.S. EPA, 2008d).

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the

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EPA developed alternative HRLs for other sensitive subpopulations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 μg/L to 47 μg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d), as part of the national primary drinking water regulatory development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- Derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon

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perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;

- Expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically fT4) that are associated with maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Review

To address the SAB recommendations, the EPA revised the existing PBPK/PD models (Lumen, Mattie, & Fisher, 2013; U.S. EPA, 2009b) to create a Biologically Based Dose Response (BBDR) model that predicts changes in thyroid hormone (i.e., T4, fT4, and T3) levels as a result of nutritional iodine intake and perchlorate exposure in women prior to pregnancy and in early gestation. The EPA developed BBDR models that included all sensitive life stages identified by the SAB, i.e., the fetus (by modeling a pregnant mother at 40 gestational weeks), neonates, and infants (SAB for the U.S. EPA, 2013, p. 19), with the pregnancy model representing the third trimester.

To assure that the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in 2017 (External Peer Reviewers for USEPA, 2017). Reviewers stressed the importance of developing an early pregnancy model when considering adverse neurodevelopmental impacts given the fetuses lack of a functioning thyroid gland until approximately 16 gestational weeks [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M

J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. The EPA considered all of the recommendations from the January 2017 peer review and implemented those needed to increase the scientific rigor of the model and modeling results. These modifications include:

- Extending the model to early pregnancy;
- Incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- Calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- Conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches to link the thyroid

hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects, using evidence from the epidemiological literature. The January 2018 peer review was largely supportive of the efforts described in the Draft Approaches Report, as evidenced by the following from the peer review final report:

> *Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).*

The EPA has revised its analysis of perchlorate health effects based upon the SAB and subsequent peer review recommendations. The analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking water (see Figure 1). The approach uses a combination of the BBDR model that simulates perchlorate impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring

[EMBED Visio.Drawing.15]

E. Identification of the Sensitive Population

The SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: "the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" (SAB for the U.S. EPA, 2013, p. 19).

The EPA's proposed MCLG aims to protect the most sensitive population, the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) identified by the SAB will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is

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sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-number>246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed

infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 µg/day). Assuming 2 or 4 µg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 µg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than 75 µg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there is a body of literature indicating that minor perturbations in thyroid hormone levels in the first trimester mother can adversely impact her offspring's neurodevelopment (USEPA, 2017):

> "[c]hildren exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Notably these effects are correlated with both degree [ADDIN EN.CITE ADDIN EN.CITE.DATA] and duration [ADDIN EN.CITE

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[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

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J</author><author>Brouwers, E P</author><author>Vader, H
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Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia
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288</pages><volume>59</volume><section>282</section><dates><year>2003</year>
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The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. As stated by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate, "the fetus is highly sensitive to any changes in thyroid hormone levels during pregnancy. It is unknown whether the neonate is similarly sensitive" [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><Prefix>CalEPA`, </Prefix><Suffix>`; p. 90</Suffix><DisplayText>(CalEPA, 2015; p. 90)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency

(CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. [HYPERLINK \l "_ENREF_9" \o "Costeira, 2011 #7"] found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, [HYPERLINK \l "_ENREF_17" \o "Henrichs, 2010 #928"] found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a sensitive population to perchlorate: preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism. Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting

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as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive population and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and
- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport,

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metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to other PBPK models and for perchlorate is simplified by the absence of metabolism.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model predicts serum thyroid hormone levels in the mother at specific gestation weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG to protect the target population with an adequate margin of safety.

The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al. (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels as the functional iodide reserve of the hypothalamic-pituitary-thyroid

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(HPT) system is limited [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>1160</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-number>1160</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206437">1160</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce,</author><author>Braverman</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice and Research: Clinical Endocrinology and Metabolism</secondary-title><alt-title>Best Pract Res Clin Endocrinol Metab</alt-title><short-title>Best Practice and Research: Clinical Endocrinology and Metabolism</short-title></titles><alt-periodical><full-title>Best Pract Res Clin Endocrinol Metab</full-title></alt-periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn>ISSN 1521-690X
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represents an intake between the 15th and 20th percentile of the population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 µg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH ranges between 4.51 and 5.41 milli-

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[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><Pages>332</Pages><DisplayText>(Alexander et al., 2017, p. 332)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-

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type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American journal of obstetrics and gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-title></periodical><pages>62-e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones[ADDIN EN.CITE ADDIN EN.CITE.DATA]. The BBDR model achieves this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allowed for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in [REF _Ref517525852 \h * MERGEFORMAT].

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Table III-[SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for Gestational Week 13 at 75 µg/day Iodine Intake at pTSH[a] = 0.398 []

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)
5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] See U.S. EPA, (2018d) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4 concentrations would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard

deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. From this distribution, the EPA chose to use the 10th percentile of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population and to assure a dose of perchlorate is selected that will protect the most sensitive population from adverse effects[5].

G. Epidemiological Literature

The SAB recommended that EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Román et al., 2013; van Mil et al., 2012). This conclusion, that maternal hypothyroxinemia is associated with offspring neurodevelopment, is also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Additionally, the American Thyroid Association also concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

As multiple sources (e.g., the American Thyroid Association, several meta-analyses and one full systematic review) concluded that maternal hypothyroxinemia is associated with adverse neurodevelopmental outcomes, and as the SAB recommended that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25), the EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes. Instead, a methodologic approach to reviewing the literature was conducted to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. Ultimately, the EPA developed a dose-response function that predicts incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

To develop the dose-response function, the EPA screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- Compatible with the sensitive life stages identified by the NRC and SAB;
- Continuous measure of thyroid hormone values (versus categorical values);
- Low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- Access to underlying data.

Using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40 papers). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia.

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[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

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Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior and other outcomes.

From these 15 papers five were selected for dose response assessment - four related to cognition [ADDIN EN.CITE ADDIN EN.CITE.DATA] and one related to behavior [ADDIN EN.CITE

<EndNote><Cite><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(Endendijk, Wijnen, Pop, & van Baar, 2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk, J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar,

A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories during pregnancy and child behavioral problems</title><secondary-title>Horm Behav</secondary-title></titles><periodical><full-title>Horm Behav</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-response assessment (e.g., dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al. (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

For each study deemed appropriate for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018d). These relationships were either presented in the paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to determine the dose of perchlorate associated with a given change in fT4. Table III-2 provides a summary of the changes in fT4 needed to produce a 1 ,2, and 3 percent decrease in the neurodevelopmental effect and corresponding perchlorate doses. These results provide a perspective on the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (as predicted by the epidemiologic literature[7]).

Table III-2. Predicted Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopmental Measure for the Population of Low-Iodine Intake Individuals Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al. (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) -$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1

[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the Approaches report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
		$(\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$							
Korevaar et al. (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8
Pop et al. (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al. (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al. (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al. (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al. (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

From the seven analyses presented, the EPA chose an independent analysis of the Korevaar et al. (2016) data (comprising 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. The reason for this selection is that an adverse health impact function can be derived for the sensitive population of interest, adjusting for the appropriate set of confounders, with a readily interpretable endpoint – intelligence quotient (IQ); the other studies do not provide one or more of these features (USEPA, 2018d). The EPA selected an independent analysis of the Korevaar data instead of the original analysis to incorporate analytical changes suggested by the 2018 peer-review panel (External Peer Reviewers for USEPA, 2018). The revised analysis controls for a more focused set of confounders (e.g., previously included variables such as infant gender, maternal parity, birthweight, mother's BMI, and gestational age at blood draw that are not related to both the

exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ[8].

The EPA has utilized a health protective approach to this analysis consistent with the SAB recommendations and the SDWA definition of the MCLG. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. The results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior and other outcomes such as autism. Of these studies, 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

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[8] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the Approaches report

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Not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. For this assessment, EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data in an attempt to minimize this uncertainty.

Intelligence is often assessed by tests that measure intelligence quotient (IQ). There are several different tests that are widely used to measure IQ, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a

standard deviation of 15 (Beres et al., 2000). Although the specific tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

IQ tests have proved to be useful for several purposes. IQ scores have shown associations with both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al. (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). In addition, IQ scores can help diagnose disorders such as mental retardation and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, one criterion for the diagnosis of mild mental retardation in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) is an IQ score between 50-55 and 70 (American Psychological Association, 2000).

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Despite the clinical use of IQ cutoffs, questions remain as to what magnitude in IQ change represents a meaningful difference. Researchers have suggested that, while an IQ point change of around one to three points may not be significant on an individual level, small changes in IQ become important when considered on the population level. For example, Bellinger (2004) argues that although a one-point change in IQ is within the standard error[9] of an individual measurement and would not be regarded as clinical disease or cause affected individuals to seek medical care, it is still highly significant on a population basis. This is because a small shift in the population distribution results in potentially large differences in the number of children in the two tails of the IQ distribution. Rogan and Ware (2003) add that relatively small changes in the mean IQ of a large number of children will dramatically increase the proportion of the population below any fixed level of concern such as an IQ of 80 and decrease the proportion above any 'gifted' level, such as 120. Nation and Gleaves (2001) argue that, assuming there is no measurement error, the standard error on a single IQ test does not matter, since errors on individual tests will be in both directions and any differences between groups will be measurable on a population basis. Carlisle et al. (2009) identified a one IQ point decrement as a *de minimus* change in IQ based on this prior literature.

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[9] The standard error of measurement for an individual test varies depending on factors such as the choice of IQ test and age at test administration. For example, the standard error for a 9 year old in the third edition of the WISC (WISC-III) is 3.35 (Bellinger, 2004).

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To select a perchlorate dose POD, the EPA selected the percent change in population IQ relating to no known or anticipated adverse effects. The EPA often uses a percentage change value in noncancer risk assessment. When assessing toxicological data, 5 percent or 10 percent, or a 0.5 to 1 standard deviation change from the mean is often used (U.S. EPA, 2012). A smaller response to inform a POD is justified and has been used when using epidemiological literature. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, U.S. EPA, 2012). Given that IQ is standardized to have a mean of 100, a 2-point decrease would be equivalent to a 2 percent decrease from the standardized mean IQ.

For the specific context of perchlorate, the EPA evaluated avoiding a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in population IQ as the basis for an MCLG. This approach was developed specifically for proposing a National Primary Drinking Water Regulation under the SDWA for perchlorate, utilizing the available literature. EPA has evaluated alternatives for deriving a perchlorate MCLG because of the uncertainty regarding the precise decrement in population IQ that represents an adverse impact. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants, since this approach might not be appropriate for conducting risks assessments or informing Agency policy for other contaminants and associated health effects. The EPA selected this approach for perchlorate to implement the general recommendations provided by the Science and Advisory Board for developing a perchlorate MCLG. The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al. (2016) study. The EPA determined that the

Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. Applying these response rates to the results from the reanalysis of Korevaar et al. (2016), results in a POD dose of 3.1 μg/kg/day for a 1 percent decrease in the population's IQ, a POD dose of 6.7 μg/kg/day for a 2 percent decrease in the population's IQ, and a POD dose of 10.8 μg/kg/day for a 3 percent decrease in the population's IQ. These PODs associated with a 1, 2 or 3 percent decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the assessment is aimed at protecting the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 μg/day and a TSH feedback loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the methodological reasons described previously, EPA believes these PODs are likely protective and should not be considered predictive.

H. Translate PODs to RfDs

When deriving an RfD the application of uncertainty/variability factors needs to be evaluated to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002).

As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed

adverse effect level (LOAEL) rather than from a NOAEL, and an incomplete database. The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., uncertainty factor for within-human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. The approach taken to derive the RfD attempts to address variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is

[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the Approaches report.

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available (i.e., no study is U.S.-based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake. Further, as discussed in section III. C the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. Further, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on the strong epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is likely because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et a., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the infant begins developing its own thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels the fetus is receiving. Given the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. This should

be accounted for with a UF because the immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. The Agency has opted to apply a UF of 3 to the POD. Section 4.4.5.3 (p 4-42) of the 2002 document recommends only reducing the intraspecies UF from a default of 10 "if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)." (USEPA, 2002). A UF of 3 was selected instead of the full 10 because the EPA has specifically attempted to model the most sensitive individuals (i.e., muted TSH feedback, low fT4 values, low-iodine intake).

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.
- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.

- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.
- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).
- The product of all the uncertainty factors (UFH) is 3 (3 x 1 x 1 x 1 x 1).

Using the POD of 6.7 µg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.23\ \frac{\mu g/kg}{day}$$

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Using an alternative POD of 3.1 µg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.03\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

I. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\ \left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 µg/kg/day for a 1 percent decrease in IQ, 2.23 µg/kg/day for a 2 percent decrease in IQ, or 3.6 µg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution of drinking water to overall perchlorate exposure.

The EPA selected a DWI estimate specific to women of childbearing age (i.e., non-pregnant, non-lactating, 15–44 years of age) (Table III-3). This decision is consistent with the analysis used in deriving an RSC_W (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the EPA's Exposure Factors Handbook (USEPA, 2011b) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis. To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate of 0.032 L/kg/day to account for variability in drinking water ingestion rates.

Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038
[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).				

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2018e). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and

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- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in more than 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (μg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The EPA then used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 μg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given

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the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III-5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.03	56%	0.032	18
2.23	80%	0.032	56
3.60	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss or a 2-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the national primary drinking water regulation. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 µg/L based on the rationale provided above. The derivation of the proposed MCLG is described in Section III and uses a point of departure based

upon a two percent decrease in IQ. The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the population. There are uncertainties (described in Section XIII) in the models used by EPA to derive the proposed and alternative MCLGs. As described in Section III, EPA has addressed these uncertainties by selecting model parameters and other factors for the derivation of the MCLG that are protective for the most sensitive life stage. EPA believes that the selection of these parameters and this point of departure assures no known or anticipated adverse effects on the health of persons and allows for an adequate margin of safety. The EPA acknowledges uncertainty with respect to the decrement of IQ that represents an adverse effect and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2018c). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate

for UCMR 1 has a minimum reporting level (MRL) of 4.0 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018f). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

Because the EPA is taking comment on alternative MCLG values of 18 µg/L and 90 µg/L the Agency has also evaluated the feasibility of setting an MCL at this level. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this level under field conditions (USEPA 2018a, 2018c). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at either 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

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When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The EPA conducted a national occurrence analysis of perchlorate in two types of public water supplies: community water systems (CWS) and non-transient, non-community water systems (NTNCWS). The EPA developed estimates of the number of entry points (and corresponding water systems) expected to exceed perchlorate levels of either 56 µg/L, 90 µg/L,

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or 18 µg/L and the number of people potentially exposed to perchlorate at different levels. The EPA is using these estimates to inform the Health Risk Reduction Cost Analysis presented in Section [REF _Ref531361870 \r \h].

The EPA used the UCMR 1 data as a key source of information for the occurrence analysis for the proposed perchlorate NPDWR. The EPA used the UCMR 1 data to estimate occurrence and exposure for the perchlorate regulatory determination. The Agency has modified the analysis of the UCMR 1 data set in response to concerns regarding UCMR 1 data quality and the actions some States have taken to regulate perchlorate in drinking water since the UCMR 1 data were generated. The EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods that provides a national assessment of perchlorate occurrence in drinking water. The UCMR 1 results are from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems. In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants (USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and

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- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 µg/L for perchlorate.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

The EPA conducted an additional data quality review in response to an Information Quality Guidelines Request for Correction submitted in 2012. As a result of this review, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the distribution system entry point. In these instances, the EPA determined the entry point sample was a better indicator of water quality provided to consumers than the source water sample. The Agency also determined that including both a source water and distribution system entry point for the same system would bias perchlorate occurrence estimates. Therefore, the EPA removed the source water sample from each pair. Thus, the final modified UCMR 1 occurrence data used for the proposed rule include 34,132 samples collected from 3,865 systems. The data include 540 measurements equal to or greater than the minimum reporting level at 149

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systems. Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

The EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two States. Massachusetts promulgated a drinking water standard for perchlorate of 2 µg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public

Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these States are now required to keep perchlorate levels in drinking water below their State limits, which are lower than the proposed MCL and alternative MCL. Therefore, UCMR 1 sampling results from systems in these States do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. Notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 μg/L	15	525	540
Sample measurements > 18 μg/L	1	16	17
Sample measurements > 56 μg/L	0	2	2
Sample measurements > 90 μg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 μg/L	8	328	336
Entry points at which measurements > 18 μg/L	1	16	17
Entry points at which measurements > 56 μg/L	0	2	2
Entry points at which measurements > 90 μg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 μg/L	8	141	149
Systems at which measurements > 18 μg/L	1	14	15
Systems at which measurements > 56 μg/L	0	2	2
Systems at which measurements > 90 μg/L	0	1	1

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UAoGFPZv","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The total row counts and counts of measurements ≥ 4 μg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 μg/L. The instances where perchlorate measurements equal or exceed either 18 μg/L, 56μg/L, or 90 μg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 μg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements > 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements > 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements > 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ChxDKgDr","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or

underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCL. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"adhRbcXq","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The Perchlorate Occurrence and Monitoring Report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"HbxFrtl3","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/

YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] describes other perchlorate data sources; including: ambient water quality data from the U.S. Geological Survey (USGS) National Water-Quality Assessment (NAWQA) program, USGS National Water Information System (NWIS) Database, the EPA's Storage and Retrieval (EPA STORET) Data Warehouse; three regional studies along the Lower Colorado River; and system monitoring data from several States and organizations.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is ''feasible'', the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, SDWA directs the EPA to determine that it is economically and technologically feasible to ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain ''criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels.'' (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. The EPA estimates that laboratory analytical monitoring costs range from $55 to $64 per each sampling event. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report ((USEPA, 2018c).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of sample analysis and data reporting. All of the proposed EPA analytical methods provide performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

If EPA issues a final NPDWR for perchlorate, the EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework. Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. Monitoring frequencies may be quarterly, annually, once every three years or once every nine years, in the case of a waiver. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point ``in the next quarter after the violation occurred (40 CFR 141.23(c)(7))." The State may allow the system to return to the routine monitoring frequency when the State determines that the system is reliably and consistently below the MCL. However, the State cannot make a determination that the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples have been collected (40 CFR 141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the State (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under the proposal, water systems may apply to the State, and States may grant, a 9-year monitoring waiver if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A State may grant a waiver for surface water systems after three rounds of annual monitoring with results less

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than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

If EPA issues a final NPDWR for perchlorate, violations of the perchlorate MCL will be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the MCL is determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than 10,000 persons must collect 4 quarterly samples during the first compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the standardized monitoring framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the second compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the standardized monitoring framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered data collected after January 1, 2020 to satisfy the initial monitoring requirements. To satisfy initial monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for non-transient non-community water systems and for community water systems serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

Community water systems must prepare and deliver an annual Consumer Confidence Report in accordance with requirements in 40 CFR 141 Subpart O.

B. What are the Public Notification Requirements?

All public water systems must give notice for all violations of national primary drinking water regulations and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation.

X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by States to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in States issuing small system variances under Section 1412(e).

A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

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- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"s9dVZckb","properties":{"formattedCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","plainCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team,

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2008)","noteIndex":0},"citationItems":[{"id":1048,"uris":["http://zotero.org/groups/945096/items/KIPNEQUM"],"uri":["http://zotero.org/groups/945096/items/KIPNEQUM"],"itemData":{"id":1048,"type":"paper-conference","title":"Castaic Lake Water Agency Operating Experience with Lead-Lag Anion Exchange for Perchlorate Removal","container-title":"Proceedings of the American Water Works Association Water Quality Technology Conference","event":"Water Quality Technology Conference","author":[{"family":"Drago","given":"J.A."},{"family":"Leserman","given":"J.R."}],"issued":{"date-parts":[["2011",11]]}}},{"id":1154,"uris":["http://zotero.org/groups/945096/items/2DBS6UYD"],"uri":["http://zotero.org/groups/945096/items/2DBS6UYD"],"itemData":{"id":1154,"type":"article","title":"News: Ion=Exchange System Removes Perchlorate","publisher":"Membrane Technology","author":[{"literal":"Membrane Technology"}],"issued":{"date-parts":[["2006",4]]}}},{"id":1125,"uris":["http://zotero.org/groups/945096/items/6WYYWFY2"],"uri":["http://zotero.org/groups/945096/items/6WYYWFY2"],"itemData":{"id":1125,"type":"report","title":"Case Study: Municipality in the State of Massachusetts","author":[{"literal":"Siemens Water Technologies"}],"issued":{"date-parts":[["2009"]]}}},{"id":1118,"uris":["http://zotero.org/groups/945096/items/5PV8GPIA"],"uri":["http://zotero.org/groups/945096/items/5PV8GPIA"],"itemData":{"id":1118,"type":"article","title":"Technical/Regulatory Guidance: Remediation Technologies for Perchlorate Contamination in Water and

Soil","URL":"http://www.eosremediation.com/download/Perchlorate/ITRC%20PERC-2.pdf","author":[{"literal":"The Interstate Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, i.e., the contaminant 'breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cxQjBTo8","properties":{"formattedCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","plainCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute,

McGuire, & Williams, 2008; Wu & Blute,
2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite

A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed. This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"I0SaZZiL","properties":{"formattedCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA

Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Ion exchange can increase the corrosivity of

treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dcLyBjzj","properties":{"formattedCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","plainCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":1079,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":1079,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1078,"uris":["http://zotero.org/groups/945096/items/BNWD5VQP"],"uri":["http://zotero.org/groups/945096/items/BNWD5VQP"],"itemData":{"id":1078,"type":"article-journal","title":"Rotation ion-exchange system removes perchlorate","page":"454A-455A","volume":"32","journalAbbreviation":"Environ. Sci. Technol.","author":[{"family":"Betts","given":"K.S."}],"issued":{"date-parts":[["1998"]]}}},{"id":1208,"uris":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"uri":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"itemData":{"id":1208,"type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] because of the addition of chloride ions and/or

removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench- and full-scale tests [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CnYkqct9","properties":{"formattedCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1019,"uris":["http://zotero.org/groups/945096/items/E5WRR4HD"],"uri":["http://zotero.org/groups/945096/items/E5WRR4HD"],"itemData":{"id":1019,"type":"article-journal","title":"Evaluation of electron donors for biological perchlorate removal highlights the importance of diverse perchlorate-reducing populations","container-title":"Environmental Science: Water Research & Technology","page":"1049-1063","volume":"2","author":[{"family":"Kotlarz","given":"N."},{"family":"Upadhyaya","given":"G."},{"family":"Togna","given":"P."},{"family":"Raskin","given":"L."}],"issued":{"date-

parts":[["2016"]]}}},{"id":1106,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1106,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR, respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 μg/L ClO4–. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 μg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-

parts":[["2015",12,1]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}},{"id":1093,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1093,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"spee

ch","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nKwIqjde","properties":{"formattedCitation":"(T. D. Webster & Crowley, 2016;

T. D. Webster & Litchfield, 2017)","plainCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield,
2017)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and
Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-
parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-
40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-
parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]. Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ISPg08cl","properties":{"formattedCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","plainCitation":"(Dugan, 2010b, 2010a; Dugan et al.,

2009)","noteIndex":0},"citationItems":[{"id":1047,"uris":["http://zotero.org/groups/945096/items/X3WWHCXS"],"uri":["http://zotero.org/groups/945096/items/X3WWHCXS"],"itemData":{"id":1047,"type":"speech","title":"The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","event-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1046,"uris":["http://zotero.org/groups/945096/items/IIXUW45F"],"uri":["http://zotero.org/groups/945096/items/IIXUW45F"],"itemData":{"id":1046,"type":"article","title":"Supporting data for presentation: The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1045,"uris":["http://zotero.org/groups/945096/items/FLVLSXCS"],"uri":["http://zotero.org/groups/945096/items/FLVLSXCS"],"itemData":{"id":1045,"type":"speech","title":"The Impact of Temperature on Anaerobic Biological Perchlorate Treatment","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dugan","given":"N.R."},{"family":"Williams","given":"D.J."},{"fam

ily":"Meyer","given":"M."},{"family":"Schneider","given":"R.R."},{"family":"Speth","given":"T.F."},{"family":"Metz","given":"D.H."}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NDoHjLOr","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"ur

i":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"f4qlOob5","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","noteIndex":0},"citationItems":[{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":111

0,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ySKwU3Em","properties":{"formattedCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield,

2017)","noteIndex":0},"citationItems":[{"id":1051,"uris":["http://zotero.org/groups/945096/items/Z7PC3BME"],"uri":["http://zotero.org/groups/945096/items/Z7PC3BME"],"itemData":{"id":1051,"type":"speech","title":"Full-Scale Biological Denitrification Plants in Germany, Austria and Poland","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dordelmann","given":"O."}],"issued":{"date-parts":[["2009",11]]}}},{"id":1026,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1026,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","t

itle":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as

permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"edXX3GgQ","properties":{"formattedCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","plainCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":985,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-

parts":[["1998"]]}}},{"id":986,"uris":["http://zotero.org/groups/945096/items/YHEV76YW"],"uri":["http://zotero.org/groups/945096/items/YHEV76YW"],"itemData":{"id":986,"type":"paper-conference","title":"Perchlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher-place":"Phoenix, AZ","event":"American Water Works Association Membrane Technology Conference","event-place":"Phoenix, AZ","author":[{"family":"Nam","given":"S."},{"family":"Kim","given":"S."},{"family":"Choi","given":"H."},{"family":"Yoon","given":""},{"family":"Silverstein","given":"J."},{"family":"Amy","given":"G."}],"issued":{"date-parts":[["2005"]]}}},{"id":992,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":992,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":991,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating

conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water. Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in [REF _Ref529958951 \h]. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"J9AlL73G","properties":{"formattedCitation":"(USEPA,

*** E.O. 12866 Review – Draft – Do Not Cite, Quote, or Release During Review***

2018a)","plainCitation":"(USEPA,

2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table X-[SEQ Table * ARABIC \s 1]: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

The SSCT listed in [REF _Ref529958951 \h] include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party

testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LHgBHn5b","properties":{"formattedCitation":"(USEPA, 1998)","plainCitation":"(USEPA, 1998)","noteIndex":0},"citationItems":[{"id":1215,"uris":["http://zotero.org/groups/945096/items/399QNBY4"],"uri":["http://zotero.org/groups/945096/items/399QNBY4"],"itemData":{"id":1215,"type":"article","title":"Variance Technology Findings for Contaminants Regulated Before 1996","publisher":"EPA 815–R– 98–003. September","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The analysis method is a comparison of

estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of median household income. [REF _Ref529959037 \h] shows the expenditure margins derived for the analysis.

Table X-[SEQ Table * ARABIC \s 1]: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2scXqyv0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"x096Tc8Y","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1225,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1225,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Rg9m81J","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018b)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018b)","noteIndex":0},"citationItems":[{"id":1226,"uris":["http://zotero.org/groups/945096/items/GTI7H6YK"],"uri":["http://zotero.org/groups/945096/items/GTI7H6YK"],"itemData":{"id":1226,"type":"article","title":"CPI--All Urban Consumers (all items), for areas under 50,000 persons","author":[{"family":"Bureau of Labor Statistics (BLS)","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

b. Affordability threshold equals 2.5 percent of MHI.

c. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fS2Ibu6t","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":163,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":163,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[REF _Ref529959069 \h] shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z6GYvRh1","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"18aKvRLD","properties":{"formattedCitation":"(USEPA,

2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":147,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":147,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-[SEQ Table * ARABIC \s 1]: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8y1WSJT4","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.

a. For perchlorate, EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum

contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public

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water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);
- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);

- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B describes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section XII.C describes this method.

Section XII.D provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2018b), which is available in the docket for the proposed rule. Section XII.E summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

The EPA estimated costs for CWS and NTNCWS to monitor and report and estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment although other treatment or nontreatment options may be lower cost or help achieve other water system objectives. EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring,

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report results, and apply for waivers. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.

1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

To estimate costs to CWSs and NTNCWSs associated with compliance monitoring and other administrative costs, the EPA generally uses the labor rate[12] for full-time treatment plant operators in CWSs from USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5g8IJ6Eh","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/FHCVSMRC"],"uri":["http://zotero.org/groups/945096/items/FHCVSMRC"],"itemData":{"id":992,"type":"article","title":"Labor Cost for National Drinking Water Rules","author":[{"family":"USEPA","given":""}],"issued":{"date-

[12] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

parts":[["2011"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of systems that currently have perchlorate at concentrations exceeding the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[13]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and nontreatment option for up to 49 different system flow rates. The EPA

[13] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018d) contains more complete discussion of the WBS models and the cost estimating approach.

generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and

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untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 μg/L the blending target would be 45 μg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-2 summarizes the labor hour assumptions for these activities.

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Table XII-2: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)

1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.

2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"C1A8zUkj","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","plainCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"uri":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"itemData":{"id":984,"type":"webpage","title":"Employer Cost for Employee Compensation -- September 2016","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-

parts":[["2016"]]}},"label":"book","suffix":"Table 3"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], for a fully loaded hourly wage rate for States of $50.67.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with [

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{"citationID":"mnzEXxZK","properties":{"formattedCitation":"(USEPA, 2008b)","plainCitation":"(USEPA,

2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":998,"uris":["http://zotero.org/groups/945096/items/QSXYHBID"],"uri":["http://zotero.org/groups/945096/items/QSXYHBID"],"itemData":{"id":998,"type":"article","title":"Draft Information Collection Request for the Disinfectants/Disinfection Byproducts, Chemical, and Radionuclides Rule","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2008",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and

annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[14]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Q6RKolIZ","properties":{"formattedCitation":"(U.S. Census Bureau, 2017b)","plainCitation":"(U.S. Census Bureau, 2017b)","noteIndex":0},"citationItems":[{"id":1000,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":1000,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA divided the total annual system-level costs by the number of households served by the system.

[14] For systems with monitoring costs only, household-level costs will be negligible.

C. *Method for Estimating Benefits*

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total

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population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rCNbGglo","properties":{"formattedCitation":"(U.S. Census Bureau, 2017a)","plainCitation":"(U.S. Census Bureau, 2017a)","noteIndex":0},"citationItems":[{"id":189,"uris":["http://zotero.org/groups/945096/items/ZM7S6H44"],"uri":["http://zotero.org/groups/945096/items/ZM7S6H44"],"itemData":{"id":189,"type":"article","title":"Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016.","URL":"https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html#ds","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7XfZyKhY","properties":{"formattedCitation":"(Martin, Hamilton, & Osterman, 2017)","plainCitation":"(Martin, Hamilton, & Osterman, 2017)","noteIndex":0},"citationItems":[{"id":186,"uris":["http://zotero.org/groups/945096/items/MY6LPDKD"],"uri":["http://zotero.org/groups/945096/items/MY6LPDKD"],"itemData":{"id":186,"type":"article","title":"Births in the United States, 2016. NCHS Data Brief No. 287","URL":"https://www.cdc.gov/nchs/data/databriefs/db287.pdf","author":[{"family":"Martin"

,"given":"J.A."},{"family":"Hamilton","given":"B.E."},{"family":"Osterman","given":"M.J.K"}]
,"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 µg/L and alternative MCLs of 18 µg/L and 90 µg/L. The first step relates changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"iqyVRL6z","properties":{"formattedCitation":"(Korevaar et al., 2016)","plainCitation":"(Korevaar et al., 2016)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-

43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI

scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Ch

aker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-3 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

Table XII-3: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2018b).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion

exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XII-E provides additional discussion of uncertainties in this analysis.

D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 μg/L, Table XII-4 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-5 summarizes the per-household cost for the system incurring treatment costs[15]. Table XII-6 summarizes the quantified benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

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[15] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

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Table XII-4: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-5: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table XII-6: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

For the alternative MCL of 18 µg/L, Table XII-7 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-8 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-9 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

Table XII-7: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H6Rcd4Hf","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.

2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-8: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"uu13kmuC","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

Table XII-9: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EN9pibZj","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-10 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-11 summarizes the per-

household cost for systems requiring treatment, which vary across the systems. Table XII-12 summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

Table XII-10: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-11: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 µg/L because treatment costs to meet an MCL of 90 µg/L are lower than the costs to meet an MCL of 56 µg/L.

Table XII-12: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Table XII-13 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between an MCL of 56 µg/L and an MCL of 18 µg/L and between an MCL of 90 µg/L and 56 µg/L.

The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 µg/L using the best available science and data, the EPA Administrator has determined that the benefits of

establishing an NPDWR for perchlorate do not justify the associated costs. In addition, the Administrator also finds that the benefits of an NPDWR at the alternative MCL values of 18 µg/L and 90 µg/L do not justify the resulting rule costs.

Table XII-13: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E0mmmXDK","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2018b). Table XIII-1

provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect
Baseline Occurrence	
UCMR1 data are more than one decade old; actual occurrence could be lower or higher because of changes over time in source water concentrations of perchlorate.	± (benefits and costs will change in the same direction)
UCMR1 data include a representative sample of small systems; the data indicates no small systems would exceed 56 µg/L or 90 µg/L although it's possible that there are small systems that have baseline perchlorate greater than either MCL.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points for systems with multiple entry points; actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
The EPA estimated entry point mean concentrations using the MRL of 4 µg/L as a substitution value for non-detection sample results; actual entry point mean concentrations could be lower.	+ (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum observed measurements that may overstate the risk of exposure to lower concentrations.	+ (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4 with increasing levels of perchlorate with lower levels of baseline fT4.	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The benefits analysis is based on a single health endpoint (see below for discussion of additional potential endpoints).	− (benefits only)

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Description	Potential effect
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)
The EPA assumed that all systems requiring treatment would implement ion exchange, which may overestimate or underestimate costs.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable 3-year monitoring period or 9-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	– (costs only)
The EPA assumed that 90 percent of ground water systems and 40 percent of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction analysis. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. The results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior and other outcomes. Of these

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studies, 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function[16].

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al. (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their

[16] A complete discussion on the selection of studies to carry through dose-response analysis is presented in section 5.3.4 of the MCLG Approaches report.

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offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al. (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

To consider the evidence on maternal thyroid hormone status on offspring neurodevelopment as a whole, the EPA also reviewed three meta-analyses that assessed the impact of maternal hypothyroxinemia on neurodevelopmental outcomes (including one full systematic review, Thompson et al., 2018). The reviews all concluded maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests [ADDIN EN.CITE ADDIN EN.CITE.DATA] when considering the entire body of evidence on this topic, not limited to the studies containing data that could potentially be used to describe the relationship between incremental changes in maternal fT4 and incremental changes in child neurodevelopmental outcomes. These conclusions are also supported by the American Thyroid Association, which concluded that the available data "appear to show an association" (p. 337, Alexander et al. 2017) between maternal hypothyroxinemia and neurodevelopment.

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In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek etl., 2017; Roman et al., 2013; Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al. (2011) and Gyllenberg et al. (2016). Although Endendijk et al. (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al. (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al. (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al. (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking. A recently published paper evaluating the EPA's BBDR model and MCLG

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Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al, 2019).

In summary, not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. For the benefits assessment, EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data in an attempt to minimize this uncertainty.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional

disorders in childhood (Man et al. 1991; Pop et al. 1999; Pop et al. 2003; Kooistra et al. 2006)" (p. 10, SAB, 2013). EPA's literature review identified relationships between maternal thyroid hormone alterations schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include effects of thyroid disorders on cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints that are not monetized in this benefits analysis (in conjunction with the previously mentioned unaccounted for variability of analysis inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above) lead to uncertainty regarding the precision of the benefits estimates in this analysis. However, it is unclear whether the analysis as a whole over- or under-estimates the benefits of a reduction of perchlorate in drinking water as the combined uncertainties could have a total effect on the estimated benefits in either direction.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues

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will be especially helpful to the EPA in developing a final rule. EPA specifically requests comment on the following topics.

- The adequacy and uncertainties of the underlying Health Effects analysis and Methodology for Deriving the Perchlorate MCLG including the models, model parameters, points of departure, uncertainty factor, and relative source contribution (Section III). The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.
- The adequacy and uncertainties of the underlying analysis of occurrence (Section VI), Treatment Technologies (Section X), and the Health Risk Reduction Cost Analysis (Section XII) described in this notice.
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's proposed finding under the SDWA that the calculated benefits associated with the proposed regulation for perchlorate, do not justify the costs as described in Section XII.D of this notice. Specifically, the Administrator finds that: *"The infrequent occurrence of perchlorate at levels of health concern achieves health risk reductions at relatively very few systems, but it imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 µg/L using the best available science and data, the EPA Administrator has determined that the benefits of establishing an NPDWR for*

perchlorate do not justify the associated costs. In addition, the Administrator also finds that the benefits of an NPDWR at the alternative MCLs of 18 µg/L and 90 µg/L do not justify the resulting rule costs."

SDWA 1412(b) allows the administrator, after notice and opportunity for public comments, to promulgate an MCL that "*maximizes health risk reduction benefits at a cost that is justified by the benefits*." Under this provision, the Agency may consider an alternative MCL that would be set at a level where benefits do justify the costs. However, the alternative MCLs evaluated by EPA would not increase benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on 1) the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), which suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern[17] and that suggest that the Administrator should find that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. Specifically, perchlorate occurrence information suggests that at an MCL of 56

[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or 90 µg/L, which are the possible levels expected to cause adverse human health effects.

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µg/L only 2 systems, (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Only one of these two systems would exceed the alternative MCL of 90 µg/L. In addition, even at an MCL of 18 µg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. If, after consideration of public comment, the EPA withdraws the perchlorate determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. In the interim, as with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using it's SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authority, as appropriate.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2018b)* is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) do not begin until after Year 3.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies,

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annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

To comment on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, the EPA has established a public docket for this rule, which includes the ICR, under Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive

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comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to

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reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 6 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2018b). Table XII-1 shows the annual compliance costs of the proposed rule on the small entities by ownership type. The EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2018b).

Table XII-1: Annual Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small PWSs

Owner Type	Small Systems	Average Annual Revenues[1]	Average Annualized Costs (as a percent of revenue)	
			3% Discount	7% Discount
Local government	22,716	$1,409,252	$88 (0.006%)	$94 (0.007%)
Private	31,510	$518,439	$88 (0.017%)	$94 (0.018%)
State government	762	$1,409,252	$88 (0.006%)	$94 (0.007%)
Federal government	600	$1,409,252	$88 (0.006%)	$94 (0.007%)
Native American	751	$1,409,252	$88 (0.006%)	$94 (0.007%)
Public/Private	1,825	$518,439	$88 (0.017%)	$94 (0.018%)
Unclassified	161	$518,439	$88 (0.017%)	$94 (0.018%)
Total	58,325	$838,719	$88 (0.010%)	$94 (0.010%)

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1. Based on Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of

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Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a public meeting in February 28, 2012 to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women

exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2018b) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply

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energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. EPA methods 314.0, 314.1, 314.2, 331.0, and

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332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (U.S. EPA 2012, NRC 2005). On May 29, 2013, the EPA received significant input from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (U.S. EPA 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking

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process for perchlorate (U.S. EPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (U.S. EPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (U.S. EPA 2013a). Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (U.S. EPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). EPA provided information to HHS officials on the draft proposed perchlorate regulation and considered HHS input **[OPEN ITEM, WE WILL UPDATE THIS SECTION TO REFLECT HHS INPUT THAT WILL BE RECEIVED DURING INTER AGENCY REVIEW]**

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List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

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Andrew R. Wheeler,

Administrator.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

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k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

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7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."

8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."

9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b),

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141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*******	*******	*******	*******

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Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM])
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.00002
*******	*******	*******	*******

*****

*****

(c)***

(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023 and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must

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collect four consecutive quarterly samples at all sampling points between January 1, 2026 and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023 and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution system may use the monitoring data from the compliance monitoring period that began between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

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(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be

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based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	Methodology[13]	EPA	ASTM[3]	SM[4] (18th, 19th ed.)	SM[4] (20th ed.)	SM Online[22]	Other
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	314.1					
	Two-Dimensional Ion Chromatography with Suppressed	314.2					

	Conductivity Detection Liquid Chromatography Electrospray Ionization Mass Spectrometry Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	331.0 332.0					
******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

*****

[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the

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Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

Contaminant	Preservative[1]	Container[2]	Time[3]
*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L

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*******	*******

*****

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

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(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

*****

(b)***

Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

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*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000 persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

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APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	Traditional MCL in mg/L	To convert for CCR, multiply by	MCL in CCR units	MCLG	Major sources in drinking water	Health effects language
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						
********	********	********	*******	*******	*******	*******

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Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]	Monitoring & testing procedure violations

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	Tier of public notice required	Citation	Tier of public notice required	Citation
*******				
B. Inorganic Chemicals (IOCs)				
*******				
14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

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Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			
C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

[2] MCL – Maximum contaminant level

PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

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2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

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7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

[FILENAME * MERGEFORMAT]

ENVI RONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 ~~ug~~µg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment

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technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, EPA is requesting comment upon ~~two~~three alternatives: -1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18 µg/L), ~~or~~ 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 µg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011 determination to regulate perchlorate in drinking water. Under this alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at [HYPERLINK "http://www.regulations.gov"]. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information

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whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit [HYPERLINK "http://www2.epa.gov/dockets/commenting-epa-dockets"].

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This proposed rule is organized as follows:

I. General Information

A. What is the EPA Proposing?

B. Does This Action Apply to Me?

II. Background

A. What is Perchlorate?

B. Statutory Authority

C. Regulatory History

III. Health Effects of Perchlorate

A. 2008 Preliminary Regulatory Determinations

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

C. Science Advisory Board Recommendations

D. Perchlorate Model Development and Peer Reviews

E. Identification of the Sensitive Population

F. BBDR Model Specification for the Sensitive Population

G. Epidemiological Literature

H. Translate POD to RfD

I. Translate RfD into an MCLG

IV. Maximum Contaminant Level Goal and Alternative

V. Maximum Contaminant Level and Alternative

VI. Occurrence

VII. Analytical Methods

VIII. Monitoring and Compliance Requirements

A. What are the Monitoring Requirements?

B. Can States Grant Monitoring Waivers?

C. *How are System MCL Violations Determined?*

D. *When Must Systems Complete Initial Monitoring?*

E. *Can Systems Use Grandfathered Data to Satisfy the Initial Monitoring Requirement?*

IX. Safe Drinking Water Act Right to Know Requirements

A. *What are the Consumer Confidence Report Requirements?*

B. *What are the Public Notification Requirements?*

X. Treatment Technologies

A. *What are the Best Available Technologies?*

B. *What are the Small System Compliance Technologies?*

XI. Rule Implementation and Enforcement

A. *What are the Requirements for Primacy?*

B. *What are the State Record Keeping Requirements?*

C. *What are the State Reporting Requirements?*

XII. Health Risk Reduction Cost Analysis

A. *Identifying Affected Entities*

B. *Method for Estimating Costs*

C. *Method for Estimating Benefits*

D. *Comparison of Costs and Benefits*

XIII. Uncertainty Analysis

XIV. Request for Comment on Proposed Rule

XV. Request for Comment on Potential Regulatory Determination Withdrawal

XVI. Administrative Requirements

A. *Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review*

B. *Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs*

C. *Paperwork Reduction Act*

D. *Regulatory Flexibility Act (RFA)*

E. *Unfunded Mandates Reform Act*

F. *Executive Order 13132: Federalism*

G. *Executive Order 13175: Consultation and Coordination with Indian Tribal Governments*

H. *Executive Order 13045: Protection of Children from Environmental Health and Safety Risks*

I. *Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use*

J. *National Technology Transfer and Advancement Act of 1995*

K. *Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations*

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and ~~two~~three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulations (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of ~~0.056 mg~~56 µg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of ~~0.056 mg~~56 µg/L.

The EPA is proposing a national primary drinking water regulation for perchlorate in accordance with its February 11, 2011 (76 FR 7762~~),~~) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

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Second, as explained in more detail below, the EPA is proposing ~~an~~two alternative ~~MCL~~/MCLG/MCL values of ~~0.018 mg~~18 µg/L~~.~~ and 90 µg/L respectively. Third, because of the low levels of occurrence of perchlorate at the levels of concern, this action also discusses and requests comment on an alternative action under which EPA would withdraw its determination to regulate perchlorate.~~-~~ Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems
State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

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Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms, which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate, used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Regulatory History

This section describes the process that led the Agency to propose an NPDWR for perchlorate. The SDWA requires the EPA to make determinations every five years whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify

priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data and encourage further research on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

Under Section 1412(b)(1)(B)(ii), the EPA must consider the occurrence data collected through the Unregulated Contaminant Monitoring Rule (UCMR). Between 2001 and 2005, the EPA required all large systems serving more than 10,000 people and a representative sample of small systems to monitor for perchlorate and 25 other contaminants under the first UCMR cycle (UCMR 1). Occurrence data generated through UCMR 1 is discussed further below.

To better understand the health effects of perchlorate, the EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate

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ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by the NIS, which may lead to decreases in T3 and T4 and increases in TSH [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The NRC recommended, and the EPA adopted, a reference dose (RfD) of 0.7 µg/kg/day. A reference dose is an estimate of a daily exposure to humans that is likely to be without an appreciable risk of adverse effects during a

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

lifetime. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment

Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA, 2008a)","plainCitation":"(USEPA, 2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation

(NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Using this health reference level of 15 µg/L the EPA also published an interim health advisory (HA) for perchlorate. HAs, which are not regulations, contain recommended concentrations of drinking water contaminants at which

adverse health effects are not anticipated to occur over specific exposure durations. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and the life stage-specific bodyweight and exposure information [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"XzGawKtq","properties":{"formattedCitation":"(USEPA, 2009a)","plainCitation":"(USEPA, 2009a)","noteIndex":0},"citationItems":[{"id":309,"uris":["http://zotero.org/groups/945096/items/ILBCYL66"],"uri":["http://zotero.org/groups/945096/items/ILBCYL66"],"itemData":{"id":309,"type":"report","title":"Inhibition of the Sodium-Iodide Symporter By Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically Based Pharmacokinetic (PBPK) Modeling (Final Report)","collection-title":"EPA/600/R-08/106A","publisher-place":"Washington, D.C.","event-place":"Washington, D.C.","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

After considering comments on the October 2008 and August 2009 notices, the EPA made a final determination in February 2011 to regulate perchlorate in drinking water [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"E1I1fclP","properties":{"formattedCitation":"(USEPA, 2011a)","plainCitation":"(USEPA, 2011a)","noteIndex":0},"citationItems":[{"id":929,"uris":["http://zotero.org/groups/945096/items/4EFIN6HN"],"uri":["http://zotero.org/groups/945096/items/4EFIN6HN"],"itemData":{"id":929,"type":"webpage","title":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","URL":"https://www.federalregister.gov/articles/2011/02/11/2011-2603/drinking-water-regulatory-determination-on-perchlorate","shortTitle":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than May 28, 2019, and finalize a NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. -The consent decree is available in the docket for today's proposed rule.

III. Health Effects

Perchlorate exposure may adversely affect human health (ATSDR 2008; SAB, 2013; Taylor et al., 2015). Specifically, perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the protein that transports iodide from blood to the thyroid gland (Greer et al., 2002; NRC, 2005; ATSDR; 2008). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB, 2013; Blount et al., 2006; Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

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Exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland. A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased thyroid stimulating hormone (TSH), the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"eF6zWm7L","properties":{"formattedCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","plainCitation":"(ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016)","noteIndex":0},"citationItems":[{"id":428,"uris":["http://zotero.org/groups/945096/items/UIANA947"],"uri":["http://zotero.org/groups/945096/items/UIANA947"],"itemData":{"id":428,"type":"bill","title":"Toxicological Profile for Perchlorates","author":[{"family":"ATSDR","given":""}],"issued":{"date-parts":[["2008"]]}}},{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid tormone levels in adolescent and adult men and

women living in the United States","container-title":"Environmental Health Perspectives","page":"1865-1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]}}},{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the national health and nutrition examination survey 2007-8","container-title":"Environmental research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors

..."","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID: 23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]}}},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy, including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide

concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L. Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ.

Health

Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels during pregnancy, including in the hypothyroxinemic range[2], have been linked to ~~many~~IQ decrements in offspring. There is also limited evidence to suggest an association with

[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Pages>10</Pages><DisplayText>(SAB, 2013, p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>] ~~in the population.~~(SAB, 2013, p.10) in the population.

other adverse neurodevelopmental outcomes ~~in offspring,~~ including ~~IQ decrements, schizophrenia,~~ ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The Agency's understanding of the effects of perchlorate on health has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of key thyroid hormones (triiodothyronine (T3) and thyroxine (T4)), and increased thyroid stimulating hormone (TSH). The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency).

Based on NRC's recommendations, the EPA adopted a perchlorate reference dose (RfD) of 0.7 μg/kg/day in 2005 (U.S. EPA, 2005). This value was based on a no observed effect level (NOEL) of 7 μg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

The EPA derived an HRL of 15 μg/L using the RfD of 0.7 μg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (primarily food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the most sensitive population, fetuses during pregnancy.

On October 10, 2008, the EPA published a preliminary negative regulatory determination for perchlorate and requested public comment on its determination that a NPDWR for perchlorate would not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA estimated that less than 1% of drinking water systems had perchlorate levels above the HRL of 15 μg/L. Therefore, the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

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In December 2008, the EPA issued an interim health advisory (15 μg/L perchlorate in drinking water) to provide guidance to State and local officials in their efforts to address perchlorate contamination in drinking water (U.S. EPA, 2008d).

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the EPA developed alternative HRLs for other sensitive subpopulations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 μg/L to 47 μg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d), as part of the national primary drinking water regulatory development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the

epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

- Derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- Expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the

smaller changes in thyroid hormones (specifically fT4) that are associated with maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

D. Perchlorate Model Development and Peer Review

To address the SAB recommendations, the EPA revised the existing PBPK/PD models (Lumen, Mattie, & Fisher, 2013; U.S. EPA, 2009b) to create a Biologically Based Dose Response (BBDR) model that predicts changes in thyroid hormone (i.e., T4, fT4, and T3) levels as a result of nutritional iodine intake and perchlorate exposure in women prior to pregnancy and in early gestation. The EPA developed BBDR models that included all sensitive life stages identified by the SAB, i.e., the fetus (by modeling a pregnant mother at 40 gestational weeks), neonates, and infants (SAB for the U.S. EPA, 2013, p. 19), with the pregnancy model representing the third trimester.

To assure that the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in 2017 (External Peer Reviewers for USEPA, 2017). Reviewers stressed the importance of developing an early pregnancy model when considering adverse neurodevelopmental impacts given the fetuses lack of a functioning thyroid gland until approximately 16 gestational weeks [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale

de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. The EPA considered all of the recommendations from the January 2017 peer review and implemented those needed to increase the scientific rigor of the model and modeling results. These modifications include:

- Extending the model to early pregnancy;
- Incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;

- Calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- Conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects, using evidence from the epidemiological literature. The January 2018 peer review was largely supportive of the efforts described in the Draft Approaches Report, as evidenced by the following from the peer review final report:

> *Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).*

The EPA has revised its analysis of perchlorate health effects based upon the SAB and subsequent peer review recommendations. The analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking

water (see Figure 1). The approach uses a combination of the BBDR model that simulates perchlorate impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring

[EMBED Visio.Drawing.15]

E. Identification of the Sensitive Population

The SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: "the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" (SAB for the U.S. EPA, 2013, p. 19).

The EPA's proposed MCLG aims to protect the most sensitive population, the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) identified by the SAB will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer

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reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 µg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-number>246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 μg/day). Assuming 2 or 4 μg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 μg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than 75 μg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there is a body of literature indicating that minor perturbations in thyroid hormone levels in the first trimester mother can adversely impact her offspring's neurodevelopment (USEPA, 2017):

> "[c]hildren exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood [ADDIN EN.CITE ADDIN EN.CITE.DATA].

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[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

Notably these effects are correlated with both degree [ADDIN EN.CITE ADDIN EN.CITE.DATA] and duration [ADDIN EN.CITE <EndNote><Cite><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(Pop et al., 2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] of maternal hypothyroxinemia" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>`; p. 10</Suffix><DisplayText>(SAB, 2013; p.

10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. As stated by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate, "the fetus is highly sensitive to any changes in thyroid hormone levels during pregnancy. It is unknown whether the neonate is similarly sensitive" [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><Prefix>CalEPA`, </Prefix><Suffix>`; p. 90</Suffix><DisplayText>(CalEPA, 2015; p. 90)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-

keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency (CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. [HYPERLINK \l "_ENREF_9" \o "Costeira, 2011 #7"] found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, [HYPERLINK \l "_ENREF_17" \o "Henrichs, 2010 #928"] found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

The SAB pointed to two lines of evidence supporting their suggestion of the infant as a sensitive population to perchlorate: preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism. Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly.

However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive population and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and
- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to other PBPK models and for perchlorate is simplified by the absence of metabolism.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model predicts serum thyroid hormone levels in the mother at specific gestation weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG to protect the target population with an adequate margin of safety.

The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al.

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(2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels as the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>1160</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-number>1160</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206437">1160</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce,</author><author>Braverman</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice and Research: Clinical Endocrinology and Metabolism</secondary-title><alt-title>Best Pract Res Clin Endocrinol Metab</alt-title><short-title>Best Practice and Research: Clinical Endocrinology and Metabolism</short-title></titles><alt-periodical><full-title>Best Pract Res Clin Endocrinol Metab</full-title></alt-periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn>ISSN 1521-690X
EISSN 1532-1908</isbn><label>755955</label><work-type>Review</work-type><urls><related-

urls><url>http://dx.doi.org/10.1016/j.beem.2009.08.009</url></related-urls></urls><electronic-resource-num>10.1016/j.beem.2009.08.009</electronic-resource-num><language>English</language></record></Cite></EndNote>]. The EPA selected an iodine intake level of 75 μg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 μg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 μg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH ranges between 4.51 and 5.41 milli-

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[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is

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defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><Pages>332</Pages><DisplayText>(Alexander et al., 2017, p. 332)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American journal of obstetrics and gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-title></periodical><pages>62-

international units per liter (mIU/L) at zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 µg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 µg/day is a better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones[ADDIN EN.CITE ADDIN EN.CITE.DATA]. The BBDR model achieves this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allowed for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

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e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in [REF _Ref517525852 \h * MERGEFORMAT].

Table III-[SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for Gestational Week 13 at 75 µg/day Iodine Intake at pTSH[a] = 0.398 []

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)
5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] See U.S. EPA, (2018d) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The

EPA assumed the variation around predicted fT4 concentrations would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. From this distribution, the EPA chose to use the 10th percentile of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population and to assure a dose of perchlorate is selected that will protect the most sensitive population from adverse effects[5].

G. Epidemiological Literature

The SAB recommended that EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Román et al., 2013; van Mil et al., 2012). This conclusion, that maternal hypothyroxinemia is associated with offspring

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

neurodevelopment, is also supported by three meta-analyses (including one full systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Additionally, the American Thyroid Association also concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

As multiple sources (e.g., the American Thyroid Association, several meta-analyses and one full systematic review) concluded that maternal hypothyroxinemia is associated with adverse neurodevelopmental outcomes, and as the SAB recommended that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25), the EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes. Instead, a methodologic approach to reviewing the literature was conducted to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. Ultimately, the EPA developed a dose-response function that predicts incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

To develop the dose-response function, the EPA screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- Compatible with the sensitive life stages identified by the NRC and SAB;
- Continuous measure of thyroid hormone values (versus categorical values);
- Low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- Access to underlying data.

Using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40 papers). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia.

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[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

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Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior~~,~~ and other outcomes ~~such as schizophrenia~~.

From these 15 papers five were selected for dose response assessment - four related to cognition [ADDIN EN.CITE ADDIN EN.CITE.DATA] and one related to behavior [ADDIN EN.CITE

<EndNote><Cite><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(Endendijk, Wijnen, Pop, & van Baar, 2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk, J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar,

A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories during pregnancy and child behavioral problems</title><secondary-title>Horm Behav</secondary-title></titles><periodical><full-title>Horm Behav</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-response assessment (e.g., dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al. (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

For each study deemed appropriate for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018d). These relationships were either presented in the paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to determine the dose of perchlorate associated with a given change in fT4. Table III-2 provides a summary of the changes in fT4 needed to produce a 1 ~~percent to~~ ,2, and 3 percent decrease in the neurodevelopmental effect and corresponding perchlorate doses. These results provide a perspective on the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (as predicted by the epidemiologic literature[7]).

[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the Approaches report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

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Table III-2. Predicted Dose of Perchlorate per 1 ~~Percent to~~, 2, and 3 Percent Decrease[a] in Neurodevelopmental Measure for the Population of Low-Iodine Intake Individuals Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 23% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c,d]			Dose of Perchlorate per 1% to 23% Decrease in Endpoint (µg/kg/day)[a,b,c,d]		
				1%	2%	3%	1%	2%	3%
Korevaar et al. (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	~~to~~ -0.25 (~~1.9% to~~ 3.8%)	-0.38 (5.7%)	1.9 ~~to 3.9~~	3.9	6.1
Korevaar et al. (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	~~to~~ -0.41 (~~3.1% to~~ (6.2%)	-0.61 (9.2%)	3.1 ~~to 6.7~~	6.7	10.8
Pop et al. (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 ~~to -0.19~~ (1.0~~% to 2.8~~%)	~~1.3 to -~~ 0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al. (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 ~~to -0.16~~ (0.9~~% to 2.4~~%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1 ~~to 2.3~~	2.3	3.5
Pop et al. (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 ~~to -0.12~~ (0.6~~% to 1.8~~%)	-0.~~8 to~~ 12 (1.~~78~~%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al. (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	~~to~~ -0.08 (~~0.45% to~~ (1.2%)	-0.12 (1.9%)	0.4 ~~to 1.1~~	1.1	1.8
Finken et al. (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	~~-0.28 to~~ -0.57 ~~(4.2% to~~ (8.5%)	-0.85[d] (12.7%)	4.4 ~~to 9.8~~	9.8	16.5[d]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 23% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c,d]			Dose of Perchlorate per 1% to 23% Decrease in Endpoint (µg/kg/day)[a,b,c,d]		
				1%	2%	3%	1%	2%	3%

[a] The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%%, 2%, or 23% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 23 point change-, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%%, 2%, or 23% change from the study mean of each measure, which for anxiety/depression is 0.01-and, 0.02, or 0.03 points, respectively, and for reaction time is 2.7-and, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b] This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75- µg/day. In all functions, fT4 is in units of pmol/L.
[c] The BBDR model with a pTSH of 0.398 was used for these analyses.
[d] ~~Ranges show results from a 1% change in the endpoint from its mean value to a 2% change in the endpoint from its mean.~~ [d] The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

From the seven analyses presented, the EPA chose an independent analysis of the Korevaar et al. (2016) data (comprising 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. The reason for this selection is that an adverse health impact function can be derived for the sensitive population of interest, adjusting for the appropriate set of confounders, with a readily interpretable endpoint – intelligence quotient (IQ); the other studies do not provide one or more of these features (USEPA, 2018d). The EPA selected an independent analysis of the Korevaar data instead of the original analysis to incorporate analytical changes suggested by the 2018 peer-review panel (External Peer Reviewers for USEPA, 2018). The revised analysis controls for a more focused set of confounders (e.g., previously included variables such as infant gender, maternal parity,

birthweight, mother's BMI, and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ[8].

The EPA has utilized a health protective approach to this analysis consistent with the SAB recommendations and the SDWA definition of the MCLG. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. The results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior and other outcomes such as autism. Of these studies, 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because

[8] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the Approaches report

the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. For this assessment, EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data in an attempt to minimize this uncertainty.

Intelligence is often assessed by tests that measure intelligence quotient (IQ). There are several different tests that are widely used to measure IQ, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is

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intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

IQ tests have proved to be useful for several purposes. IQ scores have shown associations with both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al. (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). In addition, IQ scores can help diagnose disorders such as mental retardation and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, one criterion for the diagnosis of mild mental retardation in the

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Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) is an IQ score between 50-55 and 70 (American Psychological Association, 2000).

Despite the clinical use of IQ cutoffs, questions remain as to what magnitude in IQ change represents a meaningful difference. Researchers have suggested that, while an IQ point change of around one to three points may not be significant on an individual level, small changes in IQ become important when considered on the population level. For example, Bellinger (2004) argues that although a one-point change in IQ is within the standard error[9] of an individual measurement and would not be regarded as clinical disease or cause affected individuals to seek medical care, it is still highly significant on a population basis. This is because a small shift in the population distribution results in potentially large differences in the number of children in the two tails of the IQ distribution. Rogan and Ware (2003) add that relatively small changes in the mean IQ of a large number of children will dramatically increase the proportion of the population below any fixed level of concern such as an IQ of 80 and decrease the proportion above any 'gifted' level, such as 120. Nation and Gleaves (2001) argue that, assuming there is no measurement error, the standard error on a single IQ test does not matter, since errors on individual tests will be in both directions and any differences between groups will be measurable

[9] The standard error of measurement for an individual test varies depending on factors such as the choice of IQ test and age at test administration. For example, the standard error for a 9 year old in the third edition of the WISC (WISC-III) is 3.35 (Bellinger, 2004).

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on a population basis. Carlisle et al. (2009) identified a one IQ point decrement as a *de minimus* change in IQ based on this prior literature.

To select a perchlorate dose POD, the EPA selected the percent change in population IQ relating to no known or anticipated adverse effects. The EPA often uses a percentage change value in noncancer risk assessment. When assessing toxicological data, 5 percent or 10 percent, or a 0.5 to 1 standard deviation change from the mean is often used (U.S. EPA, 2012). A smaller response to inform a POD is justified and has been used when using epidemiological literature. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, U.S. EPA, 2012).

~~Additionally, the EPA has used a specific incremental change in child IQ (e.g., 1 to 2 points IQ decrement) in considering revisions to the primary National Ambient Air Quality Standard (NAAQS) for lead (73 FR 66964).~~ Given that IQ is standardized to have a mean of 100, a ~~1 to~~ 2-point decrease would be equivalent to a ~~1 or~~ 2 percent decrease from the standardized mean IQ.

For the specific context of perchlorate, the EPA evaluated avoiding ~~both a 1 percent decrease and a 2 percent decrease in IQ as the basis for an MCLG.~~ a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in population IQ as the basis for an MCLG. This approach was developed specifically for proposing a National Primary Drinking Water Regulation under the SDWA for perchlorate, utilizing the available literature. EPA has evaluated alternatives for deriving a perchlorate MCLG because of the uncertainty regarding the precise

decrement in population IQ that represents an adverse impact. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants, since this approach might not be appropriate for conducting risks assessments or informing Agency policy for other contaminants and associated health effects. The EPA selected this approach for perchlorate to implement the general recommendations provided by the Science and Advisory Board for developing a perchlorate MCLG. The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al. (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. Applying these response rates to the results from the reanalysis of Korevaar et al. (2016), results in a POD dose of 3.1 µg/kg/day for a 1 percent decrease in the population's IQ, ~~and~~ a POD dose of 6.7 µg/kg/day for a 2 percent decrease in ~~IQ.~~ the population's IQ, and a POD dose of 10.8 µg/kg/day for a 3 percent decrease in the population's IQ. These PODs associated with a 1, 2 or ~~2~~3 percent decrease from the standardized mean IQ are calculated for the most sensitive population ~~defined as~~ . Specifically, the assessment is aimed at protecting the fetuses of mothers ~~at the low end of the distribution of fT4~~ with ~~a low~~ fT4 at the 10th percentile of a population with iodine intake of 75 µg/day and a ~~muted~~ TSH feedback ~~response. As such,~~ loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for

the methodological reasons described previously, EPA believes these PODs are likely protective and should not be considered predictive.

H. Translate PODs to RfDs

When deriving an RfD the application of uncertainty/variability factors needs to be evaluated to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002).

As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a NOAEL, and an incomplete database. The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate~~:~~.

- The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., ~~inter-individual variability)~~ ~~(~~uncertainty factor~~,~~ for within-human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. -The approach taken to derive the RfD attempts to address ~~some of the~~ variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental outcomes. -However, there is still uncertainty in the relationship between perchlorate exposure and subsequent

neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S.-based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake. Further, as discussed in section III. C the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. Further, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on the strong epidemiologic evidence that shows the relationship

[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the Approaches report.

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between first trimester maternal fT4 and neurodevelopmental outcomes. ~~This is likely because before mid-gestation, the mother is the only source of thyroid hormone for the fetus~~ [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(Morreale de Escobar et al., 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregon, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. This is likely because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et a., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it

is critical to understand the first-trimester levels. Later in gestation, when the infant begins developing its own thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels the fetus is receiving. Given the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. This should be accounted for with a UF because the immature fetal HPT axis has very limited capacity to increase output of thyroid hormones [ADDIN EN.CITE ADDIN EN.CITE.DATA]~~,~~(Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure.

~~Subsequently~~ EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. The Agency has opted to apply a UF of 3 to the POD.- Section 4.4.5.3 (p 4-42) of the 2002 document recommends only reducing the intraspecies UF from a default of 10 "if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)."

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

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(USEPA, 2002). A UF of 3 was selected instead of the full 10 because the EPA has specifically attempted to model the most sensitive individuals (i.e., muted TSH feedback, low fT4 values, low-iodine intake~~) which accounts for some of the variability within the population[12].~~).

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.
- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.
- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1

~~[12] Deriving a Data-Dependent Extrapolation Factor (DDEF) was not done in this analysis. As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)…whereas DDEFs focus on variability" (p. 7, US EPA, 2014). As described above the UFs are applied based on the uncertainties in the perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship.~~

is used. LOAELs and NOAELs were not identified or used in this approach.

- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).
- The product of all the uncertainty factors (UFH) is 3 (3 x 1 x 1 x 1 x 1).

Using the POD of 6.7 µg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.23\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 µg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.03\ \frac{\mu g/kg}{day}$$

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Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

I. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\ \left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 µg/kg/day for a 1 percent decrease in IQ ~~or~~, 2.23 µg/kg/day for a 2 percent decrease in IQ, or 3.6 µg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution of drinking water to overall perchlorate exposure.

The EPA selected a DWI estimate specific to women of childbearing age (i.e., non-pregnant, non-lactating, 15–44 years of age) (Table III-3). This decision is consistent with the analysis used in deriving an RSC_w (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age

used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the EPA's Exposure Factors Handbook (USEPA, 2011b) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis. To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate of 0.032 L/kg/day to account for variability in drinking water ingestion rates.

Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).

Individuals are exposed to perchlorate through ingestion of –both food and drinking water (ATSDR 2008, Huber et al., 2011).- In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. -Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2018e). -These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in more than 280 kinds of food and beverages commonly consumed by the U.S. population.

The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched

TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (~~ug~~µg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The EPA then used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 µg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile concentrations in TDS. This assures that highly

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exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (~~ug~~µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the ~~two~~three RfD values. Table III-5 shows the RSC values for the ~~two~~three RfD values and the corresponding MCLGs calculated using EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.03	56%	0.032	~~18 (rounded from 18.03)~~18
2.23	80%	0.032	~~56 (rounded from 55.7)~~56
3.60	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is

reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss or a 2-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and ~~Alternative~~Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the national primary drinking water regulation. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 µg/L based on the rationale provided above. The derivation of the proposed MCLG is described in Section III and uses a point of departure based upon a two percent decrease in IQ. ~~The Agency also seeks comment on an alternative MCLG of 18 µg/L which is derived using the methodology described in Section III and a one percent decrease in IQ.~~The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the population. There are uncertainties (described in Section XIII) in the models used by EPA to derive the proposed and alternative MCLGs. As described in Section III, EPA has addressed

these uncertainties by selecting model parameters and other factors for the derivation of the MCLG that are protective for the most sensitive life stage. EPA believes that the selection of these parameters and this point of departure assures no known or anticipated adverse effects on the health of persons and allows for an adequate margin of safety. The EPA acknowledges uncertainty with respect to the decrement of IQ that represents an adverse effect and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement. The Agency seeks comment on the alternative MCLG values of 18 µg/L and 90 µg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and ~~Alternative~~Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2018c). The EPA determined that setting an MCL equal to the proposed MCLG of 56 µg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4.0 µg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 µg/L (USEPA, 2018f). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 µg/L.

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Because the EPA is taking comment on ~~an~~ alternative MCLG values of 18 µg/L and 90 µg/L the Agency has also evaluated the feasibility of setting an MCL at this level. The EPA determined that the proposed MCL of 56 µg/L is feasible, therefore a higher MCL alternative such as 90 µg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 µg/L and that treatment technologies have been demonstrated to achieve this level under field conditions (USEPA 2018a, 2018c). Therefore, the EPA is requesting comment on ~~an alternative MCL of 18~~the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at either 18 µg/L ~~or~~, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction

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benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The EPA conducted a national occurrence analysis of perchlorate in two types of public water supplies: community water systems (CWS) and non-transient, non-community water systems (NTNCWS). The EPA developed estimates of the number of entry points (and corresponding water systems) expected to exceed perchlorate levels of either 56 µg/L, 90 µg/L, or 18 µg/L and the number of people potentially exposed to perchlorate at different levels. The EPA is using these estimates to inform the Health Risk Reduction Cost Analysis presented in Section [REF _Ref531361870 \r \h].

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The EPA used the UCMR 1 data as a key source of information for the occurrence analysis for the proposed perchlorate NPDWR. The EPA used the UCMR 1 data to estimate occurrence and exposure for the perchlorate regulatory determination. The Agency has modified the analysis of the UCMR 1 data set in response to concerns regarding UCMR 1 data quality and the actions some States have taken to regulate perchlorate in drinking water since the UCMR 1 data were generated. The EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods that provides a national assessment of perchlorate occurrence in drinking water. The UCMR 1 results are from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems. In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants (USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 µg/L for perchlorate.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

The EPA conducted an additional data quality review in response to an Information Quality Guidelines Request for Correction submitted in 2012. As a result of this review, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the distribution system entry point. In these instances, the EPA determined the entry point sample was a better indicator of water quality provided to consumers than the source water sample. The Agency also determined that including both a source water and distribution system entry point for the same system would bias perchlorate occurrence estimates. Therefore, the EPA removed the source water sample from each pair. Thus, the final modified UCMR 1 occurrence data used for the proposed rule include 34,132 samples collected from 3,865 systems. The data include 540 measurements equal to or greater than the minimum reporting level at 149 systems. Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems

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have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

The EPA has also reassessed the ~~UCMR1~~UCMR 1 data in light of the adoption of regulatory limits in two States. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 μg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":15

0,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these States are now required to keep perchlorate levels in drinking water below their State limits, which are lower than the proposed MCL and alternative MCL. Therefore, UCMR 1 sampling results from systems in these States do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. Notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 µg/L	15	525	540
Sample measurements ~~≥~~> 18 µg/L	1	16	17
Sample measurements ~~≥~~> 56 µg/L	0	2	2
Sample measurements > 90 µg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 µg/L	8	328	336
Entry points at which measurements ~~≥~~> 18 µg/L	1	16	17
Entry points at which measurements ~~≥~~> 56 µg/L	0	2	2
Entry points at which measurements > 90 µg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 µg/L	8	141	149
Systems at which measurements ~~≥~~> 18 µg/L	1	14	15
Systems at which measurements ~~≥~~> 56 µg/L	0	2	2
Systems at which measurements > 90 µg/L	0	1	1

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UAoGFPZv","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The total row counts and counts of measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or ~~56µg~~90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements ~~≥~~> 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements ~~≥~~> 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements ~~≥~~>18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements ~~≥~~> 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ChxDKgDr","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or ~~56µg~~90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or

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underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCL. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

[REF _Ref529966860 \h] ~~and~~ [REF _Ref529966868 \h]Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L ~~and~~, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"adhRbcXq","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z4saRTHP","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":155,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":155,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The Perchlorate Occurrence and Monitoring Report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"HbxFrtl3","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/

YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] describes other perchlorate data sources; including: ambient water quality data from the U.S. Geological Survey (USGS) National Water-Quality Assessment (NAWQA) program, USGS National Water Information System (NWIS) Database, the EPA's Storage and Retrieval (EPA STORET) Data Warehouse; three regional studies along the Lower Colorado River; and system monitoring data from several States and organizations.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is ''feasible'', the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, SDWA directs the EPA to determine that it is economically and technologically feasible to ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain ''criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels.'' (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories, and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. The EPA estimates that laboratory analytical monitoring costs range from $55 to $64 per each sampling event. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report ((USEPA, 2018c).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of sample analysis and data reporting. All of the proposed EPA analytical methods provide performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

If EPA issues a final NPDWR for perchlorate, the EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework. Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. Monitoring frequencies may be quarterly, annually, once every three years or once every nine years, in the case of a waiver. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point ``in the next quarter after the violation occurred (40 CFR 141.23(c)(7))." The State may allow the system to return to the routine monitoring frequency when the State determines that the system is reliably and consistently below the MCL. However, the State cannot make a determination that the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples have been collected (40 CFR 141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the State (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under the proposal, water systems may apply to the State, and States may grant, a 9-year monitoring waiver if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A State may grant a waiver for surface water systems after three rounds of annual monitoring with results less

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than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

If EPA issues a final NPDWR for perchlorate, violations of the perchlorate MCL will be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the MCL is determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than 10,000 persons must collect 4 quarterly samples during the first compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the standardized monitoring framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the second compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the standardized monitoring framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered data collected after January 1, 2020 to satisfy the initial monitoring requirements. To satisfy initial monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for non-transient non-community water systems and for community water systems serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

Community water systems must prepare and deliver an annual Consumer Confidence Report in accordance with requirements in 40 CFR 141 Subpart O.

B. What are the Public Notification Requirements?

All public water systems must give notice for all violations of national primary drinking water regulations and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation.

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X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by States to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in States issuing small system variances under Section 1412(e).

A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

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- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 µg/L in treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"s9dVZckb","properties":{"formattedCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","plainCitation":"(Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team,

2008)","noteIndex":0},"citationItems":[{"id":1048,"uris":["http://zotero.org/groups/945096/items/KIPNEQUM"],"uri":["http://zotero.org/groups/945096/items/KIPNEQUM"],"itemData":{"id":1048,"type":"paper-conference","title":"Castaic Lake Water Agency Operating Experience with Lead-Lag Anion Exchange for Perchlorate Removal","container-title":"Proceedings of the American Water Works Association Water Quality Technology Conference","event":"Water Quality Technology Conference","author":[{"family":"Drago","given":"J.A."},{"family":"Leserman","given":"J.R."}],"issued":{"date-parts":[["2011",11]]}}},{"id":1154,"uris":["http://zotero.org/groups/945096/items/2DBS6UYD"],"uri":["http://zotero.org/groups/945096/items/2DBS6UYD"],"itemData":{"id":1154,"type":"article","title":"News: Ion=Exchange System Removes Perchlorate","publisher":"Membrane Technology","author":[{"literal":"Membrane Technology"}],"issued":{"date-parts":[["2006",4]]}}},{"id":1125,"uris":["http://zotero.org/groups/945096/items/6WYYWFY2"],"uri":["http://zotero.org/groups/945096/items/6WYYWFY2"],"itemData":{"id":1125,"type":"report","title":"Case Study: Municipality in the State of Massachusetts","author":[{"literal":"Siemens Water Technologies"}],"issued":{"date-parts":[["2009"]]}}},{"id":1118,"uris":["http://zotero.org/groups/945096/items/5PV8GPIA"],"uri":["http://zotero.org/groups/945096/items/5PV8GPIA"],"itemData":{"id":1118,"type":"article","title":"Technical/Regulatory Guidance: Remediation Technologies for Perchlorate Contamination in Water and

Soil","URL":"http://www.eosremediation.com/download/Perchlorate/ITRC%20PERC-2.pdf","author":[{"literal":"The Interstate Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, i.e., the contaminant 'breaks through" the treatment process. At this point, the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cxQjBTo8","properties":{"formattedCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010)","plainCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute,

McGuire, & Williams, 2008; Wu & Blute,
2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite

A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed. This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"I0SaZZiL","properties":{"formattedCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":1076,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":1076,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA

Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1132,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1132,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1094,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1094,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Ion exchange can increase the corrosivity of

treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dcLyBjzj","properties":{"formattedCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","plainCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":1079,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":1079,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1078,"uris":["http://zotero.org/groups/945096/items/BNWD5VQP"],"uri":["http://zotero.org/groups/945096/items/BNWD5VQP"],"itemData":{"id":1078,"type":"article-journal","title":"Rotation ion-exchange system removes perchlorate","page":"454A-455A","volume":"32","journalAbbreviation":"Environ. Sci. Technol.","author":[{"family":"Betts","given":"K.S."}],"issued":{"date-parts":[["1998"]]}}},{"id":1208,"uris":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"uri":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"itemData":{"id":1208,"type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] because of the addition of chloride ions and/or

removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench- and full-scale tests [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CnYkqct9","properties":{"formattedCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1019,"uris":["http://zotero.org/groups/945096/items/E5WRR4HD"],"uri":["http://zotero.org/groups/945096/items/E5WRR4HD"],"itemData":{"id":1019,"type":"article-journal","title":"Evaluation of electron donors for biological perchlorate removal highlights the importance of diverse perchlorate-reducing populations","container-title":"Environmental Science: Water Research & Technology","page":"1049-1063","volume":"2","author":[{"family":"Kotlarz","given":"N."},{"family":"Upadhyaya","given":"G."},{"family":"Togna","given":"P."},{"family":"Raskin","given":"L."}],"issued":{"date-

parts":[["2016"]]}}},{"id":1106,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1106,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR, respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 μg/L ClO4–. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 μg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-

parts":[["2015",12,1]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}},{"id":1093,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1093,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"spee

ch","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nKwIqjde","properties":{"formattedCitation":"(T. D. Webster & Crowley, 2016;

T. D. Webster & Litchfield, 2017)","plainCitation":"(T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield,
2017)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and
Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-
parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-
40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-
parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]. Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ISPg08cl","properties":{"formattedCitation":"(Dugan, 2010b, 2010a; Dugan et al., 2009)","plainCitation":"(Dugan, 2010b, 2010a; Dugan et al.,

2009)","noteIndex":0},"citationItems":[{"id":1047,"uris":["http://zotero.org/groups/945096/items/X3WWHCXS"],"uri":["http://zotero.org/groups/945096/items/X3WWHCXS"],"itemData":{"id":1047,"type":"speech","title":"The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","event-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1046,"uris":["http://zotero.org/groups/945096/items/IIXUW45F"],"uri":["http://zotero.org/groups/945096/items/IIXUW45F"],"itemData":{"id":1046,"type":"article","title":"Supporting data for presentation: The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1045,"uris":["http://zotero.org/groups/945096/items/FLVLSXCS"],"uri":["http://zotero.org/groups/945096/items/FLVLSXCS"],"itemData":{"id":1045,"type":"speech","title":"The Impact of Temperature on Anaerobic Biological Perchlorate Treatment","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dugan","given":"N.R."},{"family":"Williams","given":"D.J."},{"fam

ily":"Meyer","given":"M."},{"family":"Schneider","given":"R.R."},{"family":"Speth","given":"T.F."},{"family":"Metz","given":"D.H."}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in bioreactors require nutrients to grow and effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NDoHjLOr","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"ur

i":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"f4qlOob5","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008, 2009)","noteIndex":0},"citationItems":[{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":111

0,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1116,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ySKwU3Em","properties":{"formattedCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017)","plainCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield,

2017)","noteIndex":0},"citationItems":[{"id":1051,"uris":["http://zotero.org/groups/945096/items/Z7PC3BME"],"uri":["http://zotero.org/groups/945096/items/Z7PC3BME"],"itemData":{"id":1051,"type":"speech","title":"Full-Scale Biological Denitrification Plants in Germany, Austria and Poland","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dordelmann","given":"O."}],"issued":{"date-parts":[["2009",11]]}}},{"id":1026,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1026,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1110,"uris":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"uri":["http://zotero.org/groups/945096/items/VE5JI4GQ"],"itemData":{"id":1110,"type":"report","title":"Perchlorate Removal, Destruction, and Field Monitoring Demonstration (Drinking Water - Pilot Scale)","collection-title":"ESTCP Cost and Performance Report (ER-0312)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008"]]}}},{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","t

itle":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as

permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"edXX3GgQ","properties":{"formattedCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","plainCitation":"(Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":985,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-

parts":[["1998"]]}}},{"id":986,"uris":["http://zotero.org/groups/945096/items/YHEV76YW"],"uri":["http://zotero.org/groups/945096/items/YHEV76YW"],"itemData":{"id":986,"type":"paper-conference","title":"Perchlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher-place":"Phoenix, AZ","event":"American Water Works Association Membrane Technology Conference","event-place":"Phoenix, AZ","author":[{"family":"Nam","given":"S."},{"family":"Kim","given":"S."},{"family":"Choi","given":"H."},{"family":"Yoon","given":""},{"family":"Silverstein","given":"J."},{"family":"Amy","given":"G."}],"issued":{"date-parts":[["2005"]]}}},{"id":992,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":992,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":991,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating

conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water. Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in [REF _Ref529958951 \h]. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"J9AlL73G","properties":{"formattedCitation":"(USEPA,

2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table X-[SEQ Table * ARABIC \s 1]: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

The SSCT listed in [REF _Ref529958951 \h] include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party

testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LHgBHn5b","properties":{"formattedCitation":"(USEPA, 1998)","plainCitation":"(USEPA, 1998)","noteIndex":0},"citationItems":[{"id":1215,"uris":["http://zotero.org/groups/945096/items/399QNBY4"],"uri":["http://zotero.org/groups/945096/items/399QNBY4"],"itemData":{"id":1215,"type":"article","title":"Variance Technology Findings for Contaminants Regulated Before 1996","publisher":"EPA 815–R– 98–003. September","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The analysis method is a comparison of

estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of median household income. [REF _Ref529959037 \h] shows the expenditure margins derived for the analysis.

Table X-[SEQ Table * ARABIC \s 1]: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2scXqyv0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"x096Tc8Y","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1225,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1225,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Rg9m81J","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018b)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018b)","noteIndex":0},"citationItems":[{"id":1226,"uris":["http://zotero.org/groups/945096/items/GTI7H6YK"],"uri":["http://zotero.org/groups/945096/items/GTI7H6YK"],"itemData":{"id":1226,"type":"article","title":"CPI--All Urban Consumers (all items), for areas under 50,000 persons","author":[{"family":"Bureau of Labor Statistics (BLS)","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

b. Affordability threshold equals 2.5 percent of MHI.

c. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fS2Ibu6t","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":163,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":163,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[REF _Ref529959069 \h] shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z6GYvRh1","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"18aKvRLD","properties":{"formattedCitation":"(USEPA,

2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":147,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":147,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-[SEQ Table * ARABIC \s 1]: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8y1WSJT4","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1210,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1210,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.

a. For perchlorate, EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum

contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public

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water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);
- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);

- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B describes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section XII.C describes this method.

Section XII.D provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2018b), which is available in the docket for the proposed rule. Section XII.E summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

The EPA estimated costs for CWS and NTNCWS to monitor and report and estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment although other treatment or nontreatment options may be lower cost or help achieve other water system objectives. EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring,

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report results, and apply for waivers. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.

1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

To estimate costs to CWSs and NTNCWSs associated with compliance monitoring and other administrative costs, the EPA generally uses the labor rate[13] for full-time treatment plant operators in CWSs from USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5g8IJ6Eh","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/FHCVSMRC"],"uri":["http://zotero.org/groups/945096/items/FHCVSMRC"],"itemData":{"id":992,"type":"article","title":"Labor Cost for National Drinking Water Rules","author":[{"family":"USEPA","given":""}],"issued":{"date-

[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

parts":[["2011"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of systems that currently have perchlorate at concentrations exceeding the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[14]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and nontreatment option for up to 49 different system flow rates. The EPA

[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018d) contains more complete discussion of the WBS models and the cost estimating approach.

generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and

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untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 ~~ug~~µg/L the blending target would be 45 ~~ug~~µg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-2 summarizes the labor hour assumptions for these activities.

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Table XII-2: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)

1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.

2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"C1A8zUkj","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","plainCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"uri":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"itemData":{"id":984,"type":"webpage","title":"Employer Cost for Employee Compensation -- September 2016","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-

parts":[["2016"]]}},"label":"book","suffix":"Table 3"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], for a fully loaded hourly wage rate for States of $50.67.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mnzEXxZK","properties":{"formattedCitation":"(USEPA, 2008b)","plainCitation":"(USEPA,

2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":998,"uris":["http://zotero.org/groups/945096/items/QSXYHBID"],"uri":["http://zotero.org/groups/945096/items/QSXYHBID"],"itemData":{"id":998,"type":"article","title":"Draft Information Collection Request for the Disinfectants/Disinfection Byproducts, Chemical, and Radionuclides Rule","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2008",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and

annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[15]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Q6RKolIZ","properties":{"formattedCitation":"(U.S. Census Bureau, 2017b)","plainCitation":"(U.S. Census Bureau, 2017b)","noteIndex":0},"citationItems":[{"id":1000,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":1000,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA divided the total annual system-level costs by the number of households served by the system.

[15] For systems with monitoring costs only, household-level costs will be negligible.

C. *Method for Estimating Benefits*

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science has limited this quantitative benefits assessment to ~~quantifying~~ the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total

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population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rCNbGglo","properties":{"formattedCitation":"(U.S. Census Bureau, 2017a)","plainCitation":"(U.S. Census Bureau, 2017a)","noteIndex":0},"citationItems":[{"id":189,"uris":["http://zotero.org/groups/945096/items/ZM7S6H44"],"uri":["http://zotero.org/groups/945096/items/ZM7S6H44"],"itemData":{"id":189,"type":"article","title":"Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016.","URL":"https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html#ds","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7XfZyKhY","properties":{"formattedCitation":"(Martin, Hamilton, & Osterman, 2017)","plainCitation":"(Martin, Hamilton, & Osterman, 2017)","noteIndex":0},"citationItems":[{"id":186,"uris":["http://zotero.org/groups/945096/items/MY6LPDKD"],"uri":["http://zotero.org/groups/945096/items/MY6LPDKD"],"itemData":{"id":186,"type":"article","title":"Births in the United States, 2016. NCHS Data Brief No. 287","URL":"https://www.cdc.gov/nchs/data/databriefs/db287.pdf","author":[{"family":"Martin"

,"given":"J.A."},{"family":"Hamilton","given":"B.E."},{"family":"Osterman","given":"M.J.K"}]
,"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 µg/L and alternative ~~MCL~~MCLs of 18 µg/L and 90 µg/L. The first step relates changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"iqyVRL6z","properties":{"formattedCitation":"(Korevaar et al., 2016)","plainCitation":"(Korevaar et al., 2016)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-

43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI

scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Ch

aker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-3 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

Table XII-3: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2018b).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion

exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XII-E provides additional discussion of uncertainties in this analysis.

D. Comparison of Costs and Benefits

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 μg/L, Table XII-4 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-5 summarizes the per-household cost for the system incurring treatment costs[16]. Table XII-6 summarizes the quantified benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

Table XII-4: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"00m0B8b8","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-5: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xTqTuaNv","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Table XII-6: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"T7LDdiyn","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

For the alternative MCL of 18 µg/L, Table XII-7 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-8 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-9 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

Table XII-7: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H6Rcd4Hf","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.

2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-8: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"uu13kmuC","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

Table XII-9: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EN9pibZj","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

1. EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-10 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-11 summarizes the per-

household cost for systems requiring treatment, which vary across the systems. Table XII-12 summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

Table XII-10: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

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1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-11: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

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Table XII-12: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

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Table XII-13 provides a comparison of benefits and costs for ~~both~~three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In ~~either case~~all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also shows the incremental impact on costs and benefits between ~~and~~an MCL of 56 µg/L and an MCL of 18 µg/L and between an MCL of 90 µg/L and 56 µg/L.

The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative ~~costs~~cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 ~~ug~~µg/L using the best available science and data, the EPA Administrator has determined that the benefits of

establishing an NPDWR for perchlorate do not justify the associated costs. In addition, the Administrator also finds that the benefits of an NPDWR at the alternative MCL values of 18 ~~ug~~µg/L and 90 µg/L do not justify the resulting rule costs.

Table XII-~~10~~13: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E0mmmXDK","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1217,"uris":["http://zotero.org/groups/945096/items/P9YD2GRH"],"uri":["http://zotero.org/groups/945096/items/P9YD2GRH"],"itemData":{"id":1217,"type":"article","title":"Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Detail may not sum to total because of independent rounding.

1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2018b). Table XIII-1

provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect
Baseline Occurrence	
UCMR1 data are more than one decade old; actual occurrence could be lower ~~(e.g.,~~or higher because of ~~contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated~~changes over time in source water concentrations of perchlorate.	± (benefits and costs will change in the same direction)
UCMR1 data include a representative sample of small systems; the data indicates no small systems would exceed 56 µg/L or ~~18~~90 µg/L although it's possible that there are small systems that have baseline perchlorate greater than either MCL.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points for systems with multiple entry points; actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
The EPA estimated entry point mean concentrations using the MRL of 4 µg/L as a substitution value for non-detection sample results; actual entry point mean concentrations could be lower.	+ (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum observed measurements that may overstate the risk of exposure to lower concentrations.	+ (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4 with increasing levels of perchlorate with lower levels of baseline fT4.	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The benefits analysis is based on a single health endpoint (see below for discussion of additional potential endpoints).	− (benefits only)

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Description	Potential effect
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)
The EPA assumed that all systems requiring treatment would implement ion exchange, which may overestimate or underestimate costs.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable 3-year monitoring period or 9-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	– (costs only)
The EPA assumed that 90 percent of ground water systems and 40 percent of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction analysis. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. The results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior and other outcomes ~~such as~~

~~schizophrenia.~~. Of these studies, 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function[17].

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al. (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their

[17] A complete discussion on the selection of studies to carry through dose-response analysis is presented in section 5.3.4 of the MCLG Approaches report.

offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al. (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

To consider the evidence on maternal thyroid hormone status on offspring neurodevelopment as a whole, the EPA also reviewed three meta-analyses that assessed the impact of maternal hypothyroxinemia on neurodevelopmental outcomes (including one full systematic review, Thompson et al., 2018). The reviews all concluded maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests [ADDIN EN.CITE ADDIN EN.CITE.DATA] when considering the entire body of evidence on this topic, not limited to the studies containing data that could potentially be used to describe the relationship between incremental changes in maternal fT4 and incremental changes in child neurodevelopmental outcomes. These conclusions are also supported by the American Thyroid Association, which concluded that the available data "appear to show an association" (p. 337, Alexander et al. 2017) between maternal hypothyroxinemia and neurodevelopment.

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In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek etl., 2017; Roman et al., 2013; Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al. (2011) and Gyllenberg et al. (2016). Although Endendijk et al. (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al. (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al. (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al. (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking. A recently published paper evaluating the EPA's BBDR model and MCLG

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Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al, 2019).

In summary, not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses ([HYPERLINK \l "_ENREF_47" \o "Fan, 2016 #307"]; Thompson et al., 2018 and [HYPERLINK \l "_ENREF_187" \o "Wang, 2016 #327"]), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes. The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. For the benefits assessment, EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data in an attempt to minimize this uncertainty.

There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional

disorders in childhood (Man et al. 1991; Pop et al. 1999; Pop et al. 2003; Kooistra et al. 2006)" (p. 10, SAB, 2013). EPA's literature review identified relationships between maternal thyroid hormone alterations schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include effects of thyroid disorders on cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints that are not monetized in this benefits analysis (in conjunction with the previously mentioned unaccounted for variability of analysis inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above) lead to uncertainty regarding the precision of the benefits estimates in this analysis. However, it is unclear whether the analysis as a whole over- or under-estimates the benefits of a reduction of perchlorate in drinking water as the combined uncertainties could have a total effect on the estimated benefits in either direction.

XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues

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will be especially helpful to the EPA in developing a final rule. EPA specifically requests comment on~~:~~ the following topics.

- The adequacy and uncertainties of the underlying ~~technical analysis (~~Health Effects analysis and Methodology for Deriving the Perchlorate ~~Relative Source Contribution (RSC),~~ MCLG including the models, model parameters, points of departure, uncertainty factor, and relative source contribution (Section III~~; Occurrence,~~). The proposed MCLG and MCL of 56 µg/L as well as the alternative MCLG and MCL values of 18 µg/L and of 90 µg/L.
- The adequacy and uncertainties of the underlying analysis of occurrence (Section VI~~;~~), Treatment Technologies~~,~~ (Section X), and the Health Risk Reduction Cost Analysis~~,~~ (Section XII) described in this notice.
- ~~The proposed MCLG and MCL of 56 ug/L as well as the proposed alternative MCLG and MCL of 18 ug/L.~~
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's proposed finding under the SDWA that the calculated benefits associated with the proposed regulation for perchlorate, do not justify the costs as described in Section XII.D of this notice. Specifically, the Administrator finds that: *"The infrequent occurrence of perchlorate at levels of health concern achieves health risk reductions at relatively very few systems, but it imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits*

estimated at the proposed MCL of 56 ~~ug~~µg/L using the best available science and data, the EPA Administrator has determined that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs. In addition, the Administrator also finds that the benefits of an NPDWR at the alternative ~~MCL~~MCLs of 18 ~~ug~~µg/L and 90 µg/L do not justify the resulting rule costs."

SDWA 1412(b) allows the administrator, after notice and opportunity for public comments, to promulgate an MCL that "*maximizes health risk reduction benefits at a cost that is justified by the benefits*." Under this provision, the Agency may consider an alternative MCL that would be set at a level where benefits do justify the costs. However, the alternative MCLs evaluated by EPA would not increase benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on 1) the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), which suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern[18] and that suggest that the Administrator should find that the regulation of perchlorate

[18] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 µg/L, 18 µg/L or ~~18~~90 µg/L, which are the possible levels expected to cause adverse human health effects.

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does not present a meaningful opportunity for health risk reduction for persons served by public water systems. Specifically, perchlorate occurrence information suggests that at an MCL of 56 ~~ug~~µg/L only 2 systems, (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Only one of these two systems would exceed the alternative MCL of 90 µg/L. In addition, even at an MCL of 18 ~~ug~~µg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. If, after consideration of public comment, the EPA withdraws the perchlorate determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. In the interim, as with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using it's SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authority, as appropriate.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2018b)* is available in the docket and is summarized in section XI.

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) do not begin until after Year 3.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million

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for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

To comment on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, the EPA has established a public docket for this rule, which includes the ICR, under Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to

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OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB must receive comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 µg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these

systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur monitoring costs only. Impacts on small entities are described in more detail in Chapter 6 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2018b). Table XII-1 shows the annual compliance costs of the proposed rule on the small entities by ownership type. The EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2018b).

Table XII-1: Annual Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small PWSs

Owner Type	Small Systems	Average Annual Revenues[1]	Average Annualized Costs (as a percent of revenue)	
			3% Discount	7% Discount
Local government	22,716	$1,409,252	$88 (0.006%)	$94 (0.007%)
Private	31,510	$518,439	$88 (0.017%)	$94 (0.018%)
State government	762	$1,409,252	$88 (0.006%)	$94 (0.007%)
Federal government	600	$1,409,252	$88 (0.006%)	$94 (0.007%)
Native American	751	$1,409,252	$88 (0.006%)	$94 (0.007%)
Public/Private	1,825	$518,439	$88 (0.017%)	$94 (0.018%)
Unclassified	161	$518,439	$88 (0.017%)	$94 (0.018%)
Total	58,325	$838,719	$88 (0.010%)	$94 (0.010%)

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1. Based on Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of

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Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a public meeting in February 28, 2012 to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women

exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2018b) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply

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energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. EPA methods 314.0, 314.1, 314.2, 331.0, and

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332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

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XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (U.S. EPA 2012, NRC 2005). On May 29, 2013, the EPA received significant input from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (U.S. EPA 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking

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process for perchlorate (U.S. EPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (U.S. EPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (U.S. EPA 2013a). Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (U.S. EPA 2013a).

On ~~[INSERT DATE]~~,March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). EPA provided information to HHS officials on the draft proposed perchlorate regulation and considered HHS input **[OPEN ITEM, WE WILL UPDATE THIS SECTION TO REFLECT HHS ~~CONSULTATION~~INPUT THAT WILL ~~TAKE PLACE~~BE RECEIVED DURING INTER AGENCY REVIEW]**

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List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew R. Wheeler,

Administrator.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

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k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

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7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."
8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."
9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b),

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141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*******	*******	*******	*******

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Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM])
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.00002
*******	*******	*******	*******

*****

*****

(c)***

(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023 and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must

collect four consecutive quarterly samples at all sampling points between January 1, 2026 and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023 and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution system may use the monitoring data from the compliance monitoring period that began between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

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(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020 and December 31, 2022 for community water systems serving greater than 10,000 persons and between January 1, 2023 and December 31, 2025 for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be

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based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	Methodology[13]	EPA	ASTM[3]	SM[4] (18th, 19th ed.)	SM[4] (20th ed.)	SM Online[22]	Other
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	314.1					
	Two-Dimensional Ion Chromatography with Suppressed	314.2					

	Conductivity Detection Liquid Chromatography Electrospray Ionization Mass Spectrometry Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	331.0 332.0					
******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

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[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the

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Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

Contaminant	Preservative[1]	Container[2]	Time[3]
*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L

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*******	*******

*****

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

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(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

*****

(b)***

Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

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*****

5 = Ion ~~Exchnage~~Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000 persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

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APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	Traditional MCL in mg/L	To convert for CCR, multiply by	MCL in CCR units	MCLG	Major sources in drinking water	Health effects language
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						
********	********	********	*******	*******	*******	*******

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Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]	Monitoring & testing procedure violations

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	Tier of public notice required	Citation	Tier of public notice required	Citation
*******				
B. Inorganic Chemicals (IOCs)				
*******				
14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

ED_005043_00061282-00199

Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			
C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

[2] MCL – Maximum contaminant level

PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

ED_005043_00061282-00200

2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

ED_005043_00061282-00201

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/3/2019 6:30:31 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN
Attachments: FRN Perchlorate Rule Redline for Review 4-3-19SHQ-V1.docx

Hi Eric,

Attached is the revised redline document. We are still waiting for one revision on Table III-2 which we should have ready later today. All the other requested edits have been incorporated. Once we receive any comments from Jenifer (if applicable) I will send a revised clean copy to all.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Tuesday, April 02, 2019 4:03 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Attached please find my comments. Please note that in the POD section I am asking if we can included the standard error for individual IQ tests. It looks as though one of the documents we reference includes this value but does not state what the standard error is. If we cannot find a reference for the standard error related to IQ tests we should delete the text I am suggesting we add.

I have attempted to add more rationale for our selection of the proposed MCLG and also added specific requests for comment about our methodology for deriving the MCLG.
Thank you for preparing this revised draft so quickly. Please let me know if you have questions. I have alerted Jennifer and she expects a revised draft tomorrow. Please let me know if that is not possible.
Eric

From: Christ, Lisa
Sent: Tuesday, April 02, 2019 3:32 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Thanks Sam – my comments are attached.

From: Hernandez-Quinones, Samuel
Sent: Tuesday, April 02, 2019 9:01 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: DELIBERATIVE: Revised Perchlorate FRN

DELIBERATIVE

Hi,

Attached for your review is a redline version of the revised FRN for perchlorate.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 9/12/2019 12:59:20 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: draft summary of perchlorate public comments
Attachments: Perchlorate Comment Summary V4.docx

Hi Eric,
Sam updated the summary to account for all comments and binned as you suggested. I think this adds clarity to what we recueved.

Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Thursday, September 12, 2019 8:46 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Hi Lisa,

Here is the revised summary document. It now accounts for all the comments uploaded in the docket.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, September 11, 2019 4:18 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: draft summary of perchlorate public comments -- Eric was wondering when this would be ready?
Importance: High

From: Christ, Lisa
Sent: Wednesday, September 11, 2019 12:02 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: draft summary of perchlorate public comments

Hi Sam,

Please see Eric's request below. I think he'd like to share with OW on Friday.

Thanks,
Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, September 11, 2019 12:00 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Thanks Lisa this breakdown is helpful but it pointed out to me that the 109 extensive and substantive letters don't all appear to be summarized.
I think there isn't a need to organize the commenters by organization type and there are some groups that are hard to categorize (i.e. we have ACWA as a regulated stakeholder but AWWA is a trade organization when the both represent drinking water utilities) I also think there is redundancy in the summary of the comments that I tried to eliminate in the attached.
Can the team take a look and see if there are organizations that have submitted extensive and substantive comments that we have not listed and if so please list them in the categories of support that are in the attached.

From: Christ, Lisa
Sent: Wednesday, September 11, 2019 7:46 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: draft summary of perchlorate public comments

Revised

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, September 10, 2019 4:04 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Hi Lisa,

Here is a revised version which incorporates previously suggested edits.

- We received 6 comment letters in support of the proposed rule at 56 ppb.
- I cannot categorically confirm that the mass mailing campaign was organized by any group, so I am removing that designation from the summary document.
- From the individual substantive letters
    - 1 supports withdrawal option
    - 1 supports 90 ppb option
    - 6 support 18 ppb option
    - 23 support regulation at a stricter level than 18pbb

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW

Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, September 10, 2019 1:44 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: draft summary of perchlorate public comments

Hi Sam,
As follow up can you please:

- Confirm we did not get support for regulation at 56 ppb
- Confirm if NRDC is mentioned as the originator of the mass campaign
- Count the 88 individual comments that 1- support withdrawal, 2- support regulation (at any concentration).

Let me know if you have questions
Thanks,
Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, September 10, 2019 1:30 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Also There are three categories of commenters presented

1. Support withdrawal
2. Support a stricter than proposed standard
3. Neutral

Does this mean there were no commenters in support of the proposed MCLG/MCL?

From: Burneson, Eric
Sent: Tuesday, September 10, 2019 1:27 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Thanks Lisa: My only comment is that unless the comment campaign letters clearly state they are submitting comments organized by NRDC or there is public information from NRDC clearly stating that they organized a comment campaign we should not attribute the campaign to them.
Eric

From: Christ, Lisa
Sent: Tuesday, September 10, 2019 12:27 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb

<alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: draft summary of perchlorate public comments

Eric,
Attached is a high level summary of the public comments received on the perchlorate proposal. OGC requested a summary to prepare the notice to the court requesting an extension of the consent decree final rule deadline. Let me know if you have questions or would like to discuss.
Lisa

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

NPDWR for Perchlorate Proposal: Summary of Public Comments

EPA received a total of 1,495 comments in response to its perchlorate rulemaking proposal.

Mass Mailing Campaign: 1,386 comments were received under a mass mailing campaign. These commenters oppose the proposed Maximum Contaminant Level of 56 µg/L stating that as proposed the MCL is too high to adequately protect the health of communities throughout the country.

Individuals: Eighty-one comment letters with varied levels of complexity were submitted by individuals. These letters cover a wide array of technical and policy issues regarding the perchlorate proposal (88 pages).

6 support the 56 µg/L proposal.
1 supports the 90 µg/L alternative.
6 support the 18 µg/L alternative.
23 support regulation at a level lower than 18 µg/L.
1 supports the withdrawal of the regulatory determination.
44 are in general opposition and/or out of scope.

Extensive and Substantive Comment Letters from Organizations: Twenty-eight Comment letters containing extensive and substantive technical and policy issues were submitted (657 pages). The overall recommendation of these comment letters on the regulatory proposal breakdown as follows.

- One organization did not take a position regarding regulation of perchlorate:
  - Association of State Drinking Water Administrators
- None support the proposed 56 µg/L proposal.
- None support the 90 µg/L alternative.
- Two support the 18 µg/L alternative:
  - Oregon
  - Virginia
- Fourteen support regulation at a level lower than 18 µg/L:
  - Association of California Water Agencies
  - Metropolitan Water District of Southern California
  - California
  - Massachusetts
  - New Jersey
  - New York
  - The Salt River Pima-Maricopa Indian Nation
  - The Tohono O'odham Nation
  - Alaska Community Action on Toxics
  - Environmental Defense Fund
  - Environmental Protection Network
  - Environmental Working Group
  - Natural Resources Defense Council
  - American Academy of Pediatrics
- Eleven support withdrawal of the determination to regulate perchlorate:

NPDWR for Perchlorate Proposal: Summary of Public Comments

U.S. Conference of Mayors & the National League of Cities (joint letter)
South Dakota
California Farm Bureau Federation
American Water
El Paso Water
American Chemistry Council
American Water Works Association
Association of Metropolitan Water Agencies
National Rural Water Association
Perchlorate Study Group
The Chlorine Institute

Message

From: Messier, Dawn [Messier.Dawn@epa.gov]
Sent: 4/3/2019 5:49:08 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN
Attachments: FRN Perchlorate Rule Redline for Review 4-2-19egbdmm.docx

Let's try again… doublechecked and it was the correct doc….

Dawn Messier
U.S.E.P.A.
Office of General Counsel
Water Law Office
202-564-5517

From: Burneson, Eric
Sent: Wednesday, April 03, 2019 1:45 PM
To: Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Dawn
The attached document is blank. Can you please double check.
I have asked the team to get a revised draft to Jennifer this afternoon if possible and it would be good to have your edits to fold in.
Eric

From: Messier, Dawn
Sent: Wednesday, April 03, 2019 1:39 PM
To: Wehling, Carrie <Wehling.Carrie@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Thanks everyone. I agree with Carrie's assessment below. I've also included a few comments in the latest file (with Eric's edits), attached.

Please let me know if you have any questions. Thanks! Dawn

Dawn Messier
U.S.E.P.A.
Office of General Counsel
Water Law Office
202-564-5517

From: Wehling, Carrie
Sent: Tuesday, April 02, 2019 12:00 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa

<Christ.Lisa@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Thanks, Eric, and all, for your continuing hard work on this package.

Ex. 5 Attorney Work Product (AWP)

Carrie

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

From: Burneson, Eric
Sent: Tuesday, April 02, 2019 9:46 AM
To: Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: DELIBERATIVE: Revised Perchlorate FRN

Carrie and Dawn:
Attached is a revised draft FRN that reflects the changes we have made to respond to concerns identified in preliminary discussions with reviewers. I would appreciate your review and input on the attached as we hope to submit the revised document for Inter Agency review by the end of the week.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel
Sent: Tuesday, April 02, 2019 9:01 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: DELIBERATIVE: Revised Perchlorate FRN

DELIBERATIVE

Hi,

Attached for your review is a redline version of the revised FRN for perchlorate.

Thanks

Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
Sent: 1/28/2020 7:33:14 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: FOR REVIEW: Perchlorate Reductions
Attachments: Reductions of Perchlorate in Drinking Water 1-24-20 v2.docx

Lisa & team – My additional edits are attached. I will stop by to discuss later today.

Thanks
Jennifer

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, January 27, 2020 11:23 AM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: FOR REVIEW: Perchlorate Reductions

Jennifer,
We have revised the draft document to address your edits/comments. There are a few places where we've replied in the comment bubbles. Let us know if you'd like to meet to discuss or if you have further edits/comments/questions.

Thank you,
Lisa

From: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Sent: Thursday, January 23, 2020 5:45 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: FOR REVIEW: Perchlorate Reductions

Thank you all for pulling this information together so quickly. The attached includes a number of comments, primarily around whether we have more information. I recognize that there are probably many instances where we just don't have anything else but I think there are a few places where we could find additional information. I'm happy to discuss.

Jennifer

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, January 22, 2020 4:49 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Burneson, Eric

<Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: FOR REVIEW: Perchlorate Reductions

Jennifer,
Attached is the second document requested during option selection. There are 5 PWSs of the 15 we identified as having UCMR1 results >18ppb that have not responded to our request for updated information. They are highlighted in yellow. We will continue to try, but I wanted to get this to you sooner rather than later.
Let us know if you have questions, concerns or need additional information.
Lisa

From: Christ, Lisa
Sent: Wednesday, January 22, 2020 11:42 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FOR REVIEW: Perchlorate Recommendations for PWSs

Jennifer,
During option selection on 1/9 with Administrator Wheeler, he requested OGWDW prepare two documents:

1. Recommendations for PWSs that may be concerned about perchlorate in drinking water (attached)
2. Reductions in perchlorate levels and actions to reduce levels since UCMR1 (pending)

For your review is document #1, which incorporates edits from Eric and Christina. We are working on document #2 and should have a draft for your review soon.

Let us know if you have questions, concerns or need additional information.
Lisa

Message

From: Corr, Elizabeth [Corr.Elizabeth@epa.gov]
Sent: 4/12/2019 5:51:46 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]
Subject: FW: Revised Perchlorate FRN and related items (to go TO OP today
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190412.docx; Transmittal Memo JM to DR 4-9-19.docx; Perchlorate Draft Action Memo 4-9-19.docx; image2019-04-12-134922.pdf; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx

As sent, FYI. OW folks are aware and it should be good to go today to OP. See italicized excerpt from Macara's email, sent within the last hour:

All: I just ran into Lee and got verbal approval from him that it's OK to send the package to OP. No further review here in OW is needed.

Macara

From: Corr, Elizabeth
Sent: Friday, April 12, 2019 1:45 PM
To: Lousberg, Macara <Lousberg.Macara@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Cc: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: Revised Perchlorate FRN and related items (to go TO OP today

HRRCA, transmittal, action memo, pdf of Jennifer's signature, and FRN. Pls let us know if anything else is needed to get the package to OP today. (I will be here til 3 PM.)
Many thanks.

From: Christ, Lisa
Sent: Friday, April 12, 2019 11:38 AM
To: Corr, Elizabeth <Corr.Elizabeth@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos

FYI ---

From: Christ, Lisa
Sent: Friday, April 12, 2019 10:52 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <khera.rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi Jennifer,

Attached for your transmittal to OW are the following:
The FRN for the NPDWR for Perchlorate, proposed rule (a clean and a track changes version for convenience)
Health Risk Reduction Cost Analysis
Transmittal/Action memos

Let us know if you need anything else.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, April 12, 2019 10:44 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi,

Attached are the revised clean versions of the Perchlorate FRN and HRRCA, which incorporate all the suggested edits to date (4-12-19).

Here also you will find a revised redline version which incorporates all edits and changes to the document made to the FRN since the last OW-IO review (3-11-19).

Finally, attached are the most recent version of the corresponding transmittal memos.

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 12 2010

OFFICE OF WATER

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Proposed Rule for Perchlorate in Drinking Water

FROM: Jennifer L. McLain, Acting Director
Office of Ground Water and Drinking Water

TO: David P. Ross
Assistant Administrator

Attached for your approval and transmittal to the Office of Policy is a *Federal Register* notice titled: National Primary Drinking Water Regulations: Proposed Perchlorate Rule.

This action contains a proposal to establish a Maximum Contaminant Level Goal (MCLG) of 0.056 mg/L and a National Primary Drinking Water Regulation for perchlorate that includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L. This action also includes proposed requirements for water systems to conduct monitoring and reporting on perchlorate and provide information on perchlorate to consumers. This action proposes requirements for primacy agencies that implement the public water system supervision program under SDWA. In addition, the proposal includes a list of treatment technologies to enable water systems to comply with the MCL including affordable technologies for small systems.

This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. This action also includes a request for comment on alternative MCL/MCLG values of 0.018 mg/L and 0.090 mg/L. Finally, because of the low levels of occurrence of perchlorate at the levels of concern, this action also requests comment on whether the EPA should withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

I recommend that you transmit the attached notice to the Office of Policy for interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

1. Federal Register Notice
2. Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Proposed Rule for Perchlorate in Drinking Water

FROM: Jennifer L. McLain, Acting Director
Office of Ground Water and Drinking Water

TO: David P. Ross
Assistant Administrator

Attached for your approval and transmittal to the Office of Policy is a *Federal Register* notice titled: National Primary Drinking Water Regulations: Proposed Perchlorate Rule.

This action contains a proposal to establish a Maximum Contaminant Level Goal (MCLG) of 0.056 mg/L and a National Primary Drinking Water Regulation for perchlorate that includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L. This action also includes proposed requirements for water systems to conduct monitoring and reporting on perchlorate and provide information on perchlorate to consumers. This action proposes requirements for primacy agencies that implement the public water system supervision program under SDWA. In addition, the proposal includes a list of treatment technologies to enable water systems to comply with the MCL including affordable technologies for small systems.

This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. This action also includes a request for comment on alternative MCL/MCLG values of 0.018 mg/L and 0.090 mg/L. Finally, because of the low levels of occurrence of perchlorate at the levels of concern, this action also requests comment on whether the EPA should withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

I recommend that you transmit the attached notice to the Office of Policy for interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

1. Federal Register Notice
2. Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 4/12/2019 2:52:07 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx; REDLINE - EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190412.docx; Transmittal Memo AA to OPEI 4-9-19.docx; Transmittal Memo EB to JM 4-9-19.docx; Transmittal Memo JM to DR 4-9-19.docx; Perchlorate Draft Action Memo 4-9-19.docx

Hi Jennifer,
Attached for your transmittal to OW are the following:
The FRN for the NPDWR for Perchlorate, proposed rule (a clean and a track changes version for convenience)
Health Risk Reduction Cost Analysis
Transmittal/Action memos

Let us know if you need anything else.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, April 12, 2019 10:44 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi,

Attached are the revised clean versions of the Perchlorate FRN and HRRCA, which incorporate all the suggested edits to date (4-12-19).

Here also you will find a revised redline version which incorporates all edits and changes to the document made to the FRN since the last OW-IO review (3-11-19).

Finally, attached are the most recent version of the corresponding transmittal memos.

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Proposed Rule for Perchlorate in Drinking Water for OMB Review (SAN 5555; RIN 2040-AD28)

FROM: David P. Ross
Assistant Administrator

TO: Brittany A. Bolen
Assistant Administrator

The Office of Water submits the National Primary Drinking Water Regulations: Proposed Perchlorate Rule and Economic analysis (SAN 5555; RIN 2040-AF28) to transmit to the Office of Management and Budget (OMB). This action contains a proposal to establish a Maximum Contaminant Level Goal (MCLG) of 0.056 mg/L and a National Primary Drinking Water Regulation for perchlorate that includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L. This action also includes proposed requirements for water systems to conduct monitoring and reporting on perchlorate and provide information on perchlorate to consumers. This action proposes requirements for primacy agencies that implement the public water system supervision program under SDWA. In addition, the proposal includes a list of treatment technologies to enable water systems to comply with the MCL including affordable technologies for small systems.

This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. This action also includes a request for comment on alternative MCL/MCLG values of 0.018 mg/L and 0.090 mg/L. Finally, because of the low levels of occurrence of perchlorate at the levels of concern, this action also requests comment on whether the EPA should withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

I recommend that OP transmit the attached Proposed Rule to the OMB for interagency review in accordance Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

1. Federal Register Notice
2. Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Proposed Rule for Perchlorate in Drinking Water

FROM: Eric G. Burneson, Director
Standards and Risk Management Division
Office of Ground Water and Drinking Water

TO: Jennifer L. McLain, Acting Director
Office of Ground Water and Drinking Water

Attached for your approval and transmittal to the Office of Water for review is a *Federal Register* notice titled: National Primary Drinking Water Regulations: Proposed Perchlorate Rule.

This action contains a proposal to establish a Maximum Contaminant Level Goal (MCLG) of 0.056 mg/L and a National Primary Drinking Water Regulation for perchlorate that includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L. This action also includes proposed requirements for water systems to conduct monitoring and reporting on perchlorate and provide information on perchlorate to consumers. This action proposes requirements for primacy agencies that implement the public water system supervision program under SDWA. In addition, the proposal includes a list of treatment technologies to enable water systems to comply with the MCL including affordable technologies for small systems.

This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. This action also includes a request for comment on alternative MCL/MCLG values of 0.018 mg/L and 0.090 mg/L. Finally, because of the low levels of occurrence of perchlorate at the levels of concern, this action also requests comment on whether the EPA should withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

I recommend that you approve and transmit the attached notice to the Office of Water for review. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

1. Federal Register Notice
2. Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 12/12/2018 8:31:22 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]; Ross, David P [ross.davidp@epa.gov]; Wildeman, Anna [wildeman.anna@epa.gov]
CC: McDonough, Owen [mcdonough.owen@epa.gov]; Best-Wong, Benita [Best-Wong.Benita@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Campbell, Ann [Campbell.Ann@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
Subject: Draft Perchlorate FRN
Attachments: Perchlorate Rule FRN 12-12-18-clean.docx

A holiday treat! Eric's team has done an amazing job in quickly developing a draft Perchlorate Proposed Rule. Per our expedited schedule, the attached preamble & rule are for simultaneous OW and OGC review. (We are sending to OGC separately). We are planning for a briefing with Ryan Jackson the week of January 7, 2019 with the goal of and EPA submission to OMB by the end of January. We will be working to get briefing materials to you the week of December 31, 2018. In the meantime, Eric and I will continue our conversations with Nancy Beck and Charlotte Bertrand on the technical analysis. Please let us know if you would like to have any of the supporting documents for review at any point in this process. As always, we are available for any questions or discussions.

Jennifer

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/12/2019 2:44:04 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: Revised Perchlorate FRN, HRRCA & Transmittal Memos
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx; REDLINE - EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190412.docx; Transmittal Memo AA to OPEI 4-9-19.docx; Transmittal Memo EB to JM 4-9-19.docx; Transmittal Memo JM to DR 4-9-19.docx; Perchlorate Draft Action Memo 4-9-19.docx; Perchlorate Draft Action Memo 4-9-19.docx

Hi,

Attached are the revised clean versions of the Perchlorate FRN and HRRCA, which incorporate all the suggested edits to date (4-12-19).

Here also you will find a revised redline version which incorporates all edits and changes to the document made to the FRN since the last OW-IO review (3-11-19).

Finally, attached are the most recent version of the corresponding transmittal memos.

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 12/12/2018 7:37:20 PM
To: Messier, Dawn [Messier.Dawn@epa.gov]
CC: Wehling, Carrie [Wehling.Carrie@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: FW: Revised Version - Perchlorate FRN
Attachments: Perchlorate Rule FRN 12-12-18-clean.docx

Hi Dawn,
Attached for your review is the draft perchlorate proposal. Jennifer will be transmitting it to OW today for concurrent review. Please provide comments NLT COB December 21. Let me know if you have questions concerns.

Thanks,
Lisa

From: Christ, Lisa
Sent: Wednesday, December 12, 2018 2:11 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Version - Perchlorate FRN

Jennifer –
The attached revised FRN addressed your edits and most of your comments/questions. Also, a few additional edits from Eric and Rajiv. As suggested by Eric, some of your questions are "open items" to be addressed post-OW/OGC review.
Lisa

From: Mclain, Jennifer
Sent: Tuesday, December 11, 2018 5:52 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Version - Perchlorate FRN

Lisa,
I am so impressed by the quality of the proposal your team put together. The attached includes my edits and comments/questions. If it would be helpful for you all to sit down and go over some of the later, rather than trying to respond in comment bubbles, I'm happy to do that. I am not as well versed on this information as you all so I may have made edits or comments that are not appropriate. If that is the case, please ignore the edit and don't feel the need to explain why.
Thanks much,
Jennifer

From: Christ, Lisa
Sent: Friday, December 07, 2018 3:16 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv

<Khera.Rajiv@epa.gov>
Subject: FW: Revised Version - Perchlorate FRN

Hi Jennifer,
The attached perchlorate proposal addresses my comments and Eric's. We have some additional information we are working on to provide more context for the HRRCA section. This version is ready for your and OW/OGC review. We'll fold in our additional information in the next round of edits.

Let us know if you have questions or concerns.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, December 07, 2018 3:10 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Version - Perchlorate FRN

Hi Lisa,

Attached is the revised FRN for Perchlorate.

Thanks

Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 5/23/2019 8:14:26 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: Fwd: SIGNED: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (SAN 5555)
Attachments: Perchlorate Rule OW-19-000-5459.pdf; ATT00001.htm

Congratulations!

Jennifer

Begin forwarded message:

> **From:** "Campbell, Ann" <Campbell.Ann@epa.gov>
> **To:** "Dennis, Allison" <Dennis.Allison@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Guilaran, Yu-Ting" <Guilaran.Yu-Ting@epa.gov>
> **Subject: Fwd: SIGNED: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (SAN 5555)**

Begin forwarded message:

> **From:** "Pritchard, Eileen" <Pritchard.Eileen@epa.gov>
> **To:** "Wheeler, Andrew" <wheeler.andrew@epa.gov>, "Jackson, Ryan" <jackson.ryan@epa.gov>, "Lyons, Troy" <lyons.troy@epa.gov>, "Bennett, Tate" <Bennett.Tate@epa.gov>, "White, Elizabeth" <white.elizabeth@epa.gov>, "Leopold, Matt (OGC)" <Leopold.Matt@epa.gov>, "Molina, Michael" <molina.michael@epa.gov>, "Best-Wong, Benita" <Best-Wong.Benita@epa.gov>, "Forsgren, Lee" <Forsgren.Lee@epa.gov>, "Ross, David P" <ross.davidp@epa.gov>, "Konkus, John" <konkus.john@epa.gov>, "Darwin, Henry" <darwin.henry@epa.gov>, "Bolen, Brittany" <bolen.brittany@epa.gov>, "McIntosh, Chad" <mcintosh.chad@epa.gov>, "Schiermeyer, Corry" <schiermeyer.corry@epa.gov>
> **Cc:** "Wooden-Aguilar, Helena" <Wooden-Aguilar.Helena@epa.gov>, "Grantham, Nancy" <Grantham.Nancy@epa.gov>, "Richardson, RobinH" <Richardson.RobinH@epa.gov>, "Hope, Brian" <Hope.Brian@epa.gov>, "Campbell, Ann" <Campbell.Ann@epa.gov>, "Lousberg, Macara" <Lousberg.Macara@epa.gov>, "Ruf, Christine" <Ruf.Christine@epa.gov>, "Evalenko, Sandy" <Evalenko.Sandy@epa.gov>, "Drinkard, Andrea" <Drinkard.Andrea@epa.gov>, "Sauerhage, Maggie" <Sauerhage.Maggie@epa.gov>, "Dennis, Allison" <Dennis.Allison@epa.gov>, "Wildeman, Anna" <wildeman.anna@epa.gov>, "McDonough, Owen" <mcdonough.owen@epa.gov>, "Pritchard, Eileen" <Pritchard.Eileen@epa.gov>, "Kime, Robin" <Kime.Robin@epa.gov>, "Nickerson, William" <Nickerson.William@epa.gov>, "DeBell, Kevin" <debell.kevin@epa.gov>, "Lovell, Will (William)" <lovell.william@epa.gov>, "Aguirre, Janita" <Aguirre.Janita@epa.gov>, "Bowles, Jack" <Bowles.Jack@epa.gov>, "Benevento, Douglas" <benevento.douglas@epa.gov>, "Gaines, Cynthia" <Gaines.Cynthia@epa.gov>, "Manibusan, Mary" <Manibusan.Mary@epa.gov>, "Sawyers, Andrew" <Sawyers.Andrew@epa.gov>, "Shimkin, Martha" <Shimkin.Martha@epa.gov>, "Kasat, Rakhi" <Kasat.Rakhi@epa.gov>, "Hackel, Angela" <Hackel.Angela@epa.gov>, "Nurse, Leanne"

<Nurse.Leanne@epa.gov>, "Johnson, Ann" <Johnson.Ann@epa.gov>, "Wadlington, Christina" <Wadlington.Christina@epa.gov>, "Evalenko, Sandy" <Evalenko.Sandy@epa.gov>

Subject: SIGNED: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (SAN 5555)

Good Afternoon.

Today, the Administrator signed the proposed rule entitled, **"National Primary Drinking Water Regulations: Proposed Perchlorate Rule. (SAN 5555)."**

This rule proposes to solicit public comment on the EPA' s proposal to establish a national primary drinking water regulation (NPDWR) and a non-enforceable maximum contaminant level goal (MCLG) for perchlorate under the Safe Drinking Water Act (SDWA). The proposed NPDWR includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L (56 µg/L), which is proposed to be set at a level equal to the proposed MCLG. The EPA is seeking comment in the attached notice on whether the Agency should consider setting the perchlorate MCLG and MCL at alternative values of0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). The EPA is also seeking comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water.

An additional extension was given for signature of the proposed rule until May 28, 2019. The EPA is addressing the consent decree requirements to sign a NPDWR and issue a MCLG for perchlorate in this proposed rule by May 28, 2019.

Attached is the signed and dated proposed rule. For your convenience, please go to **p. 146** for the Administrator's signature.

Please contact me if you have any questions regarding this email.

Eileen Pritchard
Special Assistant: Office of the Administrator
(202) 564-6578 (d)
pritchard.eileen@epa.gov

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141, and 142

[EPA-HQ-OW-2018-0780; FRL-XXXX-XX-OW]

RIN 2040-AF28

National Primary Drinking Water Regulations: Proposed Perchlorate Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule, request for public comment.

SUMMARY: The Environmental Protection Agency (EPA) is proposing a drinking water regulation for perchlorate and a health-based Maximum Contaminant Level Goal (MCLG) in accordance with the Safe Drinking Water Act (SDWA). The EPA is proposing to set both the enforceable Maximum Contaminant Level (MCL) for the perchlorate regulation and the perchlorate MCLG at 0.056 mg/L (56 μg/L). The EPA is proposing requirements for water systems to conduct monitoring and reporting for perchlorate and to provide information about perchlorate to their consumers through public notification and consumer confidence reports. This proposal includes requirements for primacy agencies that implement the public water system supervision program under the SDWA. This proposal also includes a list of treatment technologies that would enable water systems to comply with the MCL, including affordable compliance technologies for small systems serving 10,000 persons or less.

In addition to the proposed regulation, the EPA is requesting comment on three alternatives: 1) whether the MCL and MCLG for perchlorate should be set at 0.018 mg/L (18

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μg/L), 2) whether the MCL and MCLG for perchlorate should be set at 0.090 mg/L (90 μg/L), or 3) whether instead of issuing a national primary drinking water regulation, the EPA should withdraw the Agency's February 11, 2011, determination to regulate perchlorate in drinking water based on new information that indicates that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and there may not be a meaningful opportunity for health risk reduction through a drinking water regulation. Under this last alternative, the final action would be a withdrawal of the determination to regulate and there would be no MCLG or national primary drinking water regulation for perchlorate.

DATES: Comments must be received on or before *[insert date 60 days after publication in the* Federal Register*]*. Under the Paperwork Reduction Act (PRA), comments on the information collection provisions are best assured of consideration if the Office of Management and Budget (OMB) receives a copy of your comments on or before *[insert date 30 days after date of publication in the* Federal Register*]*.

ADDRESSES: Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2018-0780**, at http://www.regulations.gov. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from Regulations.gov. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or

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comment contents located outside of the primary submission (i.e. on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit http://www2.epa.gov/dockets/commenting-epa-dockets.

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This proposed rule is organized as follows:

I. General Information

A. What is the EPA Proposing?

B. Does This Action Apply to Me?

II. Background

A. What is Perchlorate?

B. Statutory Authority

C. Statutory Framework and Regulatory History

III. Assessment and Modeling of the Health Effects of Perchlorate

A. 2008 Preliminary Regulatory Determinations

B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

C. Science Advisory Board Recommendations

D. Perchlorate Model Development and Peer Reviews

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E. Sensitive Population for Deriving MCLG

F. BBDR Model Specification for the Sensitive Population

G. Epidemiological Literature

H. Identifying a Point of Departure for Developing the MCLG

I. Translate PODs to RfDs

J. Translate RfD into an MCLG

IV. Maximum Contaminant Level Goal and Alternatives

V. Maximum Contaminant Level and Alternatives

VI. Occurrence

VII. Analytical Methods

VIII. Monitoring and Compliance Requirements

A. What are the Monitoring Requirements?

B. Can States Grant Monitoring Waivers?

C. How are System MCL Violations Determined?

D. When Must Systems Complete Initial Monitoring?

E. Can Systems Use Grandfathered Data to Satisfy the Initial Monitoring Requirement?

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

B. What are the Public Notification Requirements?

X. Treatment Technologies

A. What are the Best Available Technologies?

ED_005043_00061621-00004

B. What are the Small System Compliance Technologies?

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

B. What are the State Record Keeping Requirements?

C. What are the State Reporting Requirements?

XII. Health Risk Reduction Cost Analysis

A. Identifying Affected Entities

B. Method for Estimating Costs

C. Method for Estimating Benefits

D. Comparison of Costs and Benefits

XIII. Uncertainty Analysis

A. Uncertainties in the MCLG Derivation

B. Uncertainties in the Economic Analysis

XIV. Request for Comment on Proposed Rule

XV. Request for Comment on Potential Regulatory Determination Withdrawal

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563 Improving Regulation and Regulatory Review

B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs

C. Paperwork Reduction Act

D. Regulatory Flexibility Act (RFA)

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E. Unfunded Mandates Reform Act

F. Executive Order 13132: Federalism

G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

I. Executive Order 13211: Actions That Significantly Affect Energy Supply, Distribution, or Use

J. National Technology Transfer and Advancement Act of 1995

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

XVIII. References

I. General Information

A. What is the EPA Proposing?

This action contains a proposal and three alternatives for public comment. First, the EPA proposes to establish a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate in public water supplies. The EPA proposes an MCLG of 56 μg/L, and to regulate perchlorate in drinking water at an enforceable maximum contaminant level (MCL) of 56 μg/L.

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The EPA is proposing an NPDWR for perchlorate in accordance with its February 11, 2011, (76 FR 7762) determination to regulate perchlorate under the SDWA. Based on the best available peer reviewed science at that time, the EPA found that perchlorate met the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

Second, as explained in more detail below, the EPA is soliciting comment on two alternative MCLG/MCL values of 18 μg/L and 90 μg/L respectively. Third, in light of new considerations that have come to the EPA's attention since it issued its positive regulatory determination in 2011, including information on lower levels of occurrence of perchlorate than the EPA had previously believed to exist and new analysis of the concentration that represents a level of health concern, this action also discusses and requests comment on an alternative action under which the EPA would withdraw its 2011 determination to regulate perchlorate. Under this alternative, there would be no MCLG or NPDWR for perchlorate.

B. Does This Action Apply to Me?

Entities that could potentially be affected include the following:

Category	Examples of potentially affected entities
Public water systems	Community water systems Non-transient, non-community water systems

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State and tribal agencies	Agencies responsible for drinking water regulatory development and enforcement

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities that could be affected by this action. To determine whether your facility or activities could be affected by this action, you should carefully examine this proposed rule. If you have questions regarding the applicability of this action to a particular entity, consult the person listed in the FOR FURTHER INFORMATION CONTACT section.

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water.

B. Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse effect on the health of persons; that are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a

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frequency and at levels of public health concern; and where in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

C. Statutory Framework and Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009.

Once listed on the CCL, the Agency continues to collect data on CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in drinking water. Section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after public comment, issue a determination whether or not to regulate at least five contaminants on the CCL. For any contaminant that the EPA determines meets the criteria for regulation, under Section 1412(b)(1)(E), the EPA must issue a proposed national primary drinking water regulation within two years and issue a final regulation 18 months after the proposal (which may be extended by 9 months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five

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years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water system. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems (CWS) and non-transient, non-community water systems (NTNCWS). The UCMR collects data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556) which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999, 2000b).

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule knows as the sodium/iodide symporter (NIS), which may lead to decreases in two hormones, thyroxine (T3) and triiodothyronine (T4) and increases in thyroid-stimulating hormone (TSH) (National Research Council (NRC), 2005b). Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the recommended National Research Council RfD of 0.7 μg/kg/day for perchlorate. The reference dose is an estimate of a daily exposure to humans that is likely to be

[1] For the purposes of this FRN, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

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without an appreciable risk of adverse effects. This RfD was based on a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability (USEPA, 2005b).

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA tentatively concluded that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day in making this conclusion (USEPA, 2008a). Based primarily on the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 μg/L. Based on this information the Agency determined that perchlorate did not occur frequently at levels of health concern. The EPA also determined that there was not a meaningful opportunity for a NPDWR to reduce health risks.

In January 2009 the EPA published an interim health advisory for perchlorate of 15 μg/L, consistent with the HRL derivation for perchlorate of 15 μg/L described above. Health Advisories are non-enforceable and non-regulatory and provide technical information to state agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health Advisories provide the public, including the most sensitive populations, with a margin of protection from a lifetime

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of exposure. For perchlorate, the health advisory was developed for subchronic exposure (USEPA 2008d).

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (74 FR 41883; USEPA, 2009a). After careful consideration of public comments on the October 2008 and August 2009 notices, on February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011a). The Agency stated then that when considering the alternative HRL benchmarks described in the 2009 notice, the likelihood of perchlorate to occur at levels of concern had significantly increased in comparison to the levels described on the 2008 preliminary negative determination. The EPA concluded that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally described in the 2008 notice.

In its 2011 determination, the Agency found that perchlorate may have an adverse effect on the health of persons, that it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and in the judgment of the Administrator, regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. As a result of the determination, and as required by Section 1412(b)(1)(E), the EPA initiated the process to develop an MCLG and NPDWR for perchlorate as described in this notice.

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In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data for systems in California and Massachusetts using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

In response to a lawsuit brought to enforce the deadlines in Section 1412(b)(1)(E), the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water no later than October 31, 2018, and finalize an NPDWR and MCLG for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose an NPDWR with a proposed MCLG for perchlorate in drinking water was later extended to May 28, 2019. The consent decree is available in the docket for today's proposed rule.

III. Assessment and Modeling of the Health Effects of Perchlorate

Perchlorate inhibits uptake of iodide into the thyroid gland by competitively binding to the NIS (ATSDR, 2008; Greer et al., 2002; NRC, 2005; SAB 2013; Taylor et al., 2013). Iodide is necessary for the synthesis of thyroid hormones and decreased iodide uptake into the thyroid can adversely affect thyroid hormone production (SAB for the U.S. EPA, 2013; Blount et al., 2006;

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Steinmaus et al., 2007, 2013, 2016, McMullen et al., 2017; Knight et al., 2018). These changes in thyroid hormone levels in a pregnant woman may be linked to changes in the neurodevelopment of her offspring (SAB for the U.S. EPA, 2013; Korevaar et al., 2016; Fan and Wu, 2016; Wang et al., 2016; Alexander et al., 2017; Thompson et al., 2018). In addition, alterations in thyroid homeostasis may impact other body systems including the reproductive (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and cardiovascular systems (Asvold et al., 2012; Sun et al., 2017).

The mode of action of perchlorate toxicity has been proposed as follows: exposure to perchlorate is known to inhibit the uptake of iodide by the thyroid gland through the NIS (NRC, 2005; SAB for the U.S. EPA, 2013). A sufficient inhibition of iodide uptake results in iodide deficiency within the thyroid. Given that T3 and T4 require iodide for production, a decrease in intra-thyroidal iodide can result in decreased production of these hormones. This could in turn result in increased TSH, the hormone that acts on the thyroid gland to stimulate iodide uptake to increase thyroid hormone production (Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; National Research Council (NRC), 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016). For populations with developing brains (e.g., fetuses, neonates, and children), disruptions in homeostatic thyroid hormone function can result in adverse neurodevelopmental effects (Alexander et al., 2017; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; SAB for the U.S. EPA, 2013). Specifically, decreased maternal thyroid hormone levels

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during pregnancy, including in the hypothyroxinemic range[2], have been linked to decrements in neurocognitive function in offspring (Alexander et al., 2017; Thompson et al., 2018; Wang et al., 2016). There is also limited evidence to suggest an association with other adverse neurodevelopmental outcomes including ADHD, expressive language delay, reduced school performance, autism, and delayed cognitive development (Alexander et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016, Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; van Mil et al., 2012).

The difficulty in estimating the likelihood and magnitude of the potential implications of perchlorate's mode of action on expressed neurodevelopmental health effects in humans exposed to perchlorate during development is the lack of robust epidemiological studies, especially in sensitive populations. Therefore, based on the known mode of action of perchlorate the Agency estimated potential health risks using a novel approach suggested by the EPA's Science Advisory Board (SAB for the U.S. EPA, 2013). The EPA's approach to estimating perchlorate risks has evolved over time with improved research and modeling capabilities. The following sections describe information sources the EPA used in its assessment as well as the regulatory process followed by the Agency in its decision making.

A. 2008 Preliminary Regulatory Determination

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[2] Maternal hypothyroxinemia is defined as TSH in the reference range and fT4 in the lower percentiles. The SAB notes that hypothyroxinemia has been defined by a "variety of cutoffs...ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" (SAB, 2013, p.10) in the population.

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In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency (NRC, 2005). A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of T3 and T4, and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., the fetuses of pregnant women who might have hypothyroidism or iodide deficiency). Based on these findings, the NRC recommended a reference dose of 0.7 μg/kg/day.

Based on NRC's analysis, the EPA established a perchlorate reference dose (RfD) of 0.7 μg/kg/day in 2005 (USEPA, 2005). This value was based on a no observed effect level (NOEL) of 7 μg/kg/day identified from a study (Greer, Goodman, Pleus, & Greer, 2002) of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability.

As discussed above, in 2008, the EPA derived an HRL of 15 μg/L using the RfD of 0.7 μg/kg/day, a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent that was derived for a pregnant woman (USEPA, 2008a) (73 FR 60262). The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (i.e., food) have been considered. The EPA's HRL was calculated to offer a margin of protection against adverse health effects to the subpopulation identified by the NAS as likely the most sensitive to the effects of perchlorate exposure, fetuses.

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B. 2009 Supplemental Request for Comment and 2011 Final Regulatory Determination

The EPA received over 33,000 comments in response to its 2008 preliminary determination to not regulate perchlorate (USEPA, 2011a). After reviewing the comments, the EPA developed alternative HRLs for other sensitive populations in addition to fetuses of pregnant women. The EPA developed alternative HRLs for 14 life stages including infants and children. The EPA also evaluated the occurrence of perchlorate at levels above these alternative HRLs using the UCMR 1 occurrence data.

The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) for each of the 14 life stages evaluated. The resulting HRLs ranged from 1 μg/L to 47 μg/L. In August 2009, the EPA published a supplemental request for comment with the new analysis and HRLs (74 FR 41883; USEPA, 2009a). After careful consideration of public comments, on February 11, 2011, the EPA published its final determination to regulate perchlorate (76 FR 7762; USEPA, 2011a).

C. Science Advisory Board Recommendations

As required by Section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. The SAB recommended the following:

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- derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon perchlorate's mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

This SAB-proposed framework would incorporate the previous endpoint of iodide uptake inhibition that was the basis for the RfD as part of a broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes. It also focuses on the smaller changes in thyroid hormones (specifically free T4 (fT4)) that are associated with maternal hypothyroxinemia and subsequent adverse neurodevelopmental health effects rather than the significant changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism.

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D. Perchlorate Model Development and Peer Reviews

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, i.e., breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). In addition to estimating effects on breast fed infants, several reviewers recommended that the EPA shift the primary focus of its analysis to modeling the exposure implications to the fetus during early pregnancy. This was based on the knowledge that fetuses lack a functioning thyroid gland until approximately 16 gestational weeks and the substantial epidemiological evidence linking early pregnancy low fT4 levels with adverse neurodevelopmental outcomes (Endendijk et al., 2017, Korevaar et al., 2016; Morreale de Escobar, Obregón, & Escobar del Rey, 2004, Pop et al., 1999; Pop et al., 2003). Specifically, the SAB recommended that the EPA use specific sensitive populations to develop the MCLG for perchlorate: "the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" (SAB for the U.S. EPA, 2013, p. 19).

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The EPA considered all recommendations from the 2017 peer review. The previously developed BBDR model describing perchlorate's effects in the third trimester (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b) was calibrated only for that phase of pregnancy, not for the first trimester, and lacked a description of TSH signaling (feedback) that becomes significant as individuals become hypothyroxinemic or hypothyroid. In particular, this signaling was considered necessary to accurately predict responses of women with very low iodine intake, which was also part of the 2017 peer review recommendations. Therefore, the Lumen et al., (2009b) model needed to be revised to address these recommendations and the EPA implemented those changes needed to increase the scientific rigor of the model and modeling results. These modifications include:

- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The EPA convened a second independent peer review panel in January 2018 to evaluate these updates to the BBDR model. The EPA also presented several approaches in the draft *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (MCLG Approaches Report) to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using

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evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018). The 2018 peer review identified a variety of strengths and limitations of the modeling (to be discussed in more detail later in this notice). The peer review panel was largely supportive of the efforts described in the MCLG Approaches Report, as evidenced by the following from the peer review final report:

> *Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG (External Peer Reviewers for U.S. EPA, 2018, p. 2).*

The EPA also presented an alternative, population-based approach evaluating the shift in the proportion of the population that would fall below a hypothyroxinemic cut point, given exposure to perchlorate (Section 7 of the MCLG Approaches Report). This approach does not directly connect the BBDR output to a neurodevelopmental endpoint. However, for pregnant women in early pregnancy, this shift could be related to avoiding an increase in the population of offspring's risk of adverse neurodevelopmental impacts. The 2018 peer review identified strengths associated with this approach, including

> *1) the central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; 2) this approach encompasses a variety of adverse*

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neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and 3) this approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an adverse neurodevelopmental effect. (External Peer Reviewers for U.S. EPA, 2018, p. 7)

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for an MCLG based on this approach to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The peer-review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. The EPA is requesting public comment in Section XIV on the adequacies and uncertainties of the methodology to derive the MCLG including the decision not to pursue this population-based approach for setting the MCLG.

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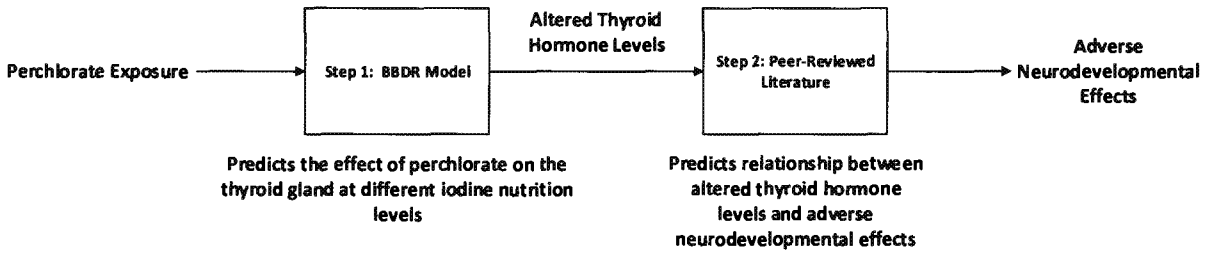
Based on the comments of the peer reviewers, the EPA's final analysis informing the derivation of the MCLG and benefits of avoided perchlorate exposure is based upon a 2-step approach to modeling the neurodevelopmental effects on offspring of pregnant women exposed to perchlorate in drinking water (see Figure 1). In summary, because of the known mode of action, the lack of epidemiological studies particularly in the sensitive populations and the direction of the SAB to use a "data-driven approach [which] represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages" (p. 2, SAB 2013 for U.S. EPA), the EPA uses a combination of the BBDR model that simulates perchlorate potential impacts on maternal thyroid hormones during pregnancy and the epidemiology literature that relates incremental changes in maternal thyroid hormones to neurodevelopmental outcomes in children. The following sections describe the approach in greater detail, highlighting each step in which decisions and assumptions were made.

Figure 1. Two-Step Modeling Approach to Link Maternal Perchlorate Exposure to Measurable Adverse Neurodevelopmental Impacts in Offspring



Note: Process figure does not imply the strength of scientific evidence.

E. Sensitive Population for Deriving MCLG

SDWA 1412(b)(4)(A) requires MCLGs to be set at a concentration in water "at which no known or anticipated adverse effects on the health of persons occur and which allows an

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adequate margin of safety." SDWA 1412(b)(3)(C)(V) further requires that the EPA "consider the effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." The EPA has interpreted these requirements to establish MCLGs that avoid adverse effects within the portions of the population that are at greater risk of adverse effects from exposure to the contaminant. The EPA is proposing an MCLG that is developed to protect the fetuses of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 μg/kg/day), low fT4 levels (i.e., 10th percentile of an fT4 distribution for individuals with 75 μg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual). The choice of this population is consistent with discussion by the NRC (2005), and the SAB (2013). The EPA believes that by protecting this population, the other sensitive populations (i.e., breast- and bottle-fed infants) will also be protected. This conclusion is based on the EPA's analysis of predictions of the impact of perchlorate on fT4 levels from the original EPA BBDR model (which was peer reviewed in January of 2017) and an analysis of the literature on the connection between altered thyroid hormones in these life stages, and neurodevelopmental outcomes.

The EPA's original BBDR model demonstrated that perchlorate had minimal impact on the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even at doses as high as 20 μg/kg/day. Specifically, the model demonstrated that "the range of iodine levels in formula is

sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" (USEPA, 2017; p. 73). As a result of these findings the EPA concluded that any MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced at given doses of perchlorate for both the breast-fed infant and the first trimester pregnant mother at varying doses of iodine intake[3] (50 to 100 μg/day). Assuming 2 or 4 μg/kg/day of perchlorate, the first trimester hypothyroxinemic pregnant mother has a greater percent change in fT4 compared to the 30 and 60 day breast-fed infant at all maternal iodine intake levels evaluated, except for the 30 day breast-fed infant of a mother consuming only 50 μg/day iodine. However, given that the original BBDR model did not have a TSH feedback loop, T4, fT4, T3 and fT3 predictions for lactating mothers with less than 75 μg/day iodine intake were considered highly uncertain because the thyroid hormone levels had fallen into the hypothyroid range.

The Agency found that there are reports in the scientific literature suggesting that minor perturbations in thyroid hormone levels in the first trimester mother may adversely impact her offspring's neurodevelopment. Specifically, some studies show that children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) have a higher risk of reduced levels of global and specific cognitive abilities, as well as increased rates of behavior

[3]Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this feedback loop, this comparison is done with the feedback loop turned off.

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problems including greater dysregulation in early infancy and attentional disorders in childhood (Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Man, Brown, & Serunian, 1991; Pop et al., 2003; Pop et al., 1999). Notably these effects are correlated with both degree (Henrichs et al., 2010; Pop et al., 1999) and duration (Pop et al., 2003) of maternal hypothyroxinemia (SAB for the U.S. EPA, 2013, p. 10).

The EPA did not find analogous evidence linking minor perturbations in thyroid hormones during infancy to adverse neurodevelopmental outcomes in infants. This finding is consistent with conclusions by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate (California Environmental Protection Agency, 2011, p. 90).

Specifically, two studies evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. Costeira et al., (2011) found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels. However, the authors found that neonatal thyroid status (measured on day 3 after birth) did not influence development. Additionally, Henrichs et al., (2010) found in their evaluation that although maternal hypothyroxinemia was associated with language delay and nonverbal cognitive delay, the neonatal thyroid status (thyroid hormones measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

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The SAB pointed to two lines of evidence supporting their suggestion of the infant as a potentially sensitive population to perchlorate: preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB for the U.S. EPA, 2013). Thus, sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the best evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants are in individuals with significant thyroid deficiencies manifesting as clinical conditions (e.g., THOP and congenital hypothyroidism). It is unclear and unknown if minor perturbations in thyroid hormones in infants, such as those that could be caused by environmental levels of perchlorate, would result in adverse neurodevelopmental outcomes similar to those seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Given the lack of evidence demonstrating minor perturbations in infant fT4 levels as being associated with neurodevelopmental outcomes, the EPA has concluded that it is appropriate to derive the perchlorate MCLG to protect the first trimester fetus of a pregnant mother with low-iodine intake. The EPA concludes that an MCLG calculated to offer a margin of protection against adverse health effects to these fetuses targets the most sensitive lifestage and will be protective of other potentially sensitive life stages as well.

F. BBDR Model Specification for the Sensitive Population

The BBDR model used to develop the proposed MCLG has two main components:

- a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of perchlorate and iodide; and

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- a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, including fT4.

The pharmacokinetic model component contains a physiological description of a human mother and fetus during pregnancy (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter of the mother) in association with a particular exposure scenario (route of exposure, age, dose level). This component of the model is similar to many other PBPK models. Because perchlorate does not undergo metabolism in vivo (Clewell et al., 2007), potential uncertainty from this factor of the model is avoided since it does not need to be described.

The pharmacodynamic component of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect.

Thus, the BBDR model estimates serum thyroid hormone levels in the mother at specific gestational weeks, given specific levels of iodine intake, the TSH feedback loop strength, and perchlorate doses. As noted above, to be health protective the EPA chose to model a sensitive individual (an adult woman with low iodine through the first trimester of pregnancy) to derive an MCLG, thereby protecting both this target sensitive population with an adequate margin of safety and those who are less sensitive with an even larger margin of safety.

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The BBDR model simulates perchlorate's impact on thyroid hormones at each gestational week from conception to week 16. To derive the MCLG, the EPA selected outputs for gestational week 13 to correspond with the thyroid hormone data reported in Korevaar et al., (2016), which is the basis for the Agency's quantitative relationship between maternal thyroid hormone levels and neurodevelopmental impacts.

Individuals with low iodine intake have increased sensitivity to perchlorate's impact on thyroid hormone levels because the functional iodide reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited (Blount et al., 2006, Steinmaus et al., 2007; Leung, Pearce, & Braverman, 2010). The EPA selected an iodine intake level of 75 μg/day to simulate an individual with low-iodine intake. This value represents an intake between the 15th and 20th percentile of the women of child bearing age population distribution of estimated iodine intake from the National Health and Nutrition Examination Survey (NHANES). The EPA considered using a lower iodine intake level of 50 μg/day, which represents approximately the 5th percentile of the NHANES distribution. At 50 μg/day of iodine intake, however, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[4] (TSH ranges between 4.51 and 5.41 milli-international units per liter (mIU/L) at

[4] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism (Alexander et al., 2017). Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" (Alexander et al., 2017, p. 332). ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. (2008) is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of gestational weeks 15 and 16) to determine the presence of hypothyroidism.

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zero dose of perchlorate when evaluating gestational weeks 12 or 13). In contrast, at 75 μg/day iodine, the BBDR modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. Thus, the intake of 75 μg/day is a better approximation of the sensitive population – the offspring of pregnant women who have low fT4.

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones (Blount et al., 2006; Steinmaus et al., 2013, 2016). The EPA designed the BBDR model to depict this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. The BBDR model allows for variability in the strength of the TSH feedback by varying these parameters with a variable called "pTSH." For the MCLG analysis, the EPA used a pTSH value of 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). This value represents an assumption that sensitive individuals with high TSH and average fT4 levels exist, and this is because the stimulus strength of TSH is proportionally weaker. The EPA chose to use a low TSH feedback coefficient to ensure the MCLG is protective of the sensitive population.

Example output from the BBDR model for gestational week 13 and a low TSH feedback coefficient is presented in Table III-1.

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Table III-1. Summary of BBDR Model Results for fT4 Levels: Pregnant Women at Gestational Week 13, Assuming Low (75 µg/day) Iodine Intake and with Muted TSH feedback strength[a]

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)[b] (% decrease from 0 dose)			
	2.5th	5th	10th	50th
0	5.57	6.09	6.70	8.84
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)
5	5.25 (-5.73%)	5.77 (-5.23%)	6.38 (-4.76%)	8.52 (-3.60%)
6	5.19 (-6.73%)	5.72 (-6.14%)	6.33 (-5.59%)	8.47 (-4.23%)
7	5.14 (-7.69%)	5.66 (-7.02%)	6.27 (-6.39%)	8.41 (-4.84%)

[a] pTSH = 0.398; see USEPA, (2018b) for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67. All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestation week and did not account for variation in perchlorate and iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (e.g. Blount et al., 2007) and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3). The EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

When modeling changes in fT4, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. Therefore, to predict the impact of perchlorate exposure on the population distribution of fT4 for the identified sensitive population, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values based on fT4 data from studies that were used to calibrate the BBDR model (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA assumed the variation around predicted fT4

concentrations for women with low fT4 of childbearing age would likely be close to normal after accounting for perchlorate and iodine intake, and thus estimated a combined standard deviation (SD) using the distributional information from each of the studies (C. Li et al., 2014; Männistö et al., 2011; Zhang et al., 2016). The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model. To protect the most sensitive population from adverse effects, the EPA chose to use the 10th percentile from this distribution of baseline fT4 to conduct its analyses to account for variability in thyroid hormones in the population[5].

G. Epidemiological Literature

The SAB recommended that the EPA integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies. There is substantial epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes, including those related to both cognition and behavior (Costeira et al., 2011; Finken, van Eijsden, Loomans, Vrijkotte, & Rotteveel, 2013; Ghassabian et al., 2014; Gyllenberg et al., 2016; Henrichs et al., 2010; Júlvez et al., 2013; Kooistra, Crawford, van Baar, Brouwers, & Pop, 2006; Korevaar et al., 2016; Y. Li et al., 2010; Oostenbroek et al., 2017; Päkkilä et al., 2015; Pop et al., 2003, 1999; Roman et al., 2013; van Mil et al., 2012). These individual studies showing that maternal hypothyroxinemia is associated with offspring neurodevelopment are also supported by three meta-analyses (including one full

[5] For a discussion on the details of the BBDR model, including uncertainties associated with the model the reader is directed to section 3.5 of the MCLG Approaches Report.

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systematic review), all of which conclude maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests when considering the entire body of evidence on this topic (Fan & Wu, 2016; Thompson et al., 2018; Wang et al., 2016). Additionally, the American Thyroid Association concludes that "overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring" (Alexander et al., 2017, p. 337).

The EPA did not conduct a full systematic review and weight of evidence evaluation between maternal thyroid hormones and neurodevelopmental outcomes given: 1) the body of scientific literature regarding this association, and 2) the SAB recommendation that the EPA "consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations" (p. 25). Instead, the EPA conducted a "methodologic approach to reviewing the literature" to evaluate the body of literature on this topic. This approach assisted in extrapolating the relationship modeled by the BBDR model to neurodevelopmental outcomes by concentrating on studies that allowed for evaluation of incremental changes in fT4 as they relate to incremental changes in neurodevelopmental outcomes. More specifically, the EPA only used studies that had sufficient data to show a quantitative relationship between maternal fT4 and a neurodevelopmental outcome. The EPA acknowledges that by not giving any weight to the studies that did not show a quantitative relationship between fT4 and neurodevelopmental outcomes, the Agency may be overestimating the dose of perchlorate that may be associated with adverse neurodevelopmental outcomes. This is a health protective decision that adds to the margin of safety.

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Ultimately, the EPA developed a dose-response function that estimates incremental changes in a neurodevelopmental endpoint based on a given change in thyroid hormone concentration (fT4), which could be linked to a given dose of perchlorate using the BBDR model.

The specifics of this "methodologic approach to reviewing the literature" follow. First, the EPA identified and screened the available 71 epidemiological studies, which potentially pertained to altered maternal thyroid hormone levels and offspring neurodevelopment to identify candidates based on the following criteria:

- compatible with the sensitive life stages identified by the NRC and SAB;
- continuous measure of thyroid hormone values (versus categorical values);
- low risk of bias based on analysis using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool score; and
- access to underlying data.

Second, using these screening steps, the EPA categorized all 71 studies into three groups. One group consisted of studies that were not compatible[6] with extending the BBDR model (40

[6] For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results. Another reason for exclusion at this stage include that the study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

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studies). Another group consisted of papers that were relevant to the pertinent life stages but did not have data from which a dose-response analysis could be conducted (15 studies). This includes studies that compared differences between groups, for example studies of offspring of mothers with hypothyroxinemia versus offspring of mothers without hypothyroxinemia. Consequently, these studies may have provided insight into the maternal thyroid hormone and offspring neurodevelopment relationship but did not have enough information to develop a continuous dose-response function. The last group of papers had data that may inform a dose-response function (16 studies). This last group of papers included publications that may have had categorical analyses but also presented data that assessed fT4 as a continuous variable and the outcome of interest. In most instances, the continuous fT4 variable encompassed the full range for fT4 and not just the hypothyroxinemic range. After excluding one paper due to a high risk of bias (Kastakina et al., 2006) 15 papers remained that potentially had dose-response data between a continuous measure of fT4 and various neurodevelopmental outcomes describing cognition, behavior and other outcomes. The EPA notes that by selecting the papers that potentially had dose response data the Agency is deviating from the systematic weight of evidence review approach to identify those studies that the SAB recommended we examine to derive the MCLG.

Third, from these 15 papers five were selected for dose response assessment - four related to cognition (Finken et al., 2013; Korevaar et al., 2016; Pop et al., 2003, 1999) and one related to behavior (Endendijk, Wijnen, Pop, & van Baar, 2017). The other ten papers were excluded for a variety of reasons including updated analyses being presented in a different paper for which dose-response analysis was being conducted, lack of all the data needed to complete a dose-

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response assessment (e.g., dose-response results were presented as "per standard deviation of fT4" but the standard deviation needed to fully interpret the results for a continuous function was not presented in the paper, statistical methods presented in the paper were insufficient to allow for the derivation of a concentration response function), or a lack of a relationship between maternal fT4 as a continuous variable and the outcome of interest evaluated in the paper. For example, Noten et al., (2015) found a relationship between maternal hypothyroxinemia and offspring arithmetic test performance. However, maternal fT4 as a continuous variable across the entire fT4 range was not associated with arithmetic test performance. Given this null finding, as well as the lack of published literature evaluating maternal fT4 as a continuous variable and arithmetic test performance, it would be difficult for the Agency to justify setting an MCLG based on changes in this endpoint.

As laid out for the peer reviewers, for each study that met the criteria identified above for dose-response modeling, a relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment was derived (see USEPA, 2018b). These relationships were either presented in the original published paper or derived by the EPA through either the digitization of figures or through re-analysis of data provided by the study authors. The EPA used the upper effect estimate (the upper bound of the 95th percent confidence interval) from each study to assure consideration of the populations likely to be at greater risk from the dose of perchlorate associated with a given change in fT4.

Table III-2 provides a summary of the changes in fT4 predicted to produce a 1, 2, and 3 percent decrease in any given neurodevelopmental effect and corresponding perchlorate doses.

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The choice of 1, 2, and 3% is based on the analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI). Specifically, a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points) equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively (Endendijk et al., 2017; Finken et al., 2013).

These results provide the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (derived from the epidemiologic literature[7]).

Table III-2. Estimated Dose of Perchlorate per 1, 2, and 3 Percent Decrease[a] in Neurodevelopment for the Population of Low-Iodine Intake Women of Reproductive Age Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al., (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β1 = 33.8 (9.8, 57.8) β2 = -6.2 (-10.6, -1.9)	-0.13 (1.9%)	-0.25 (3.8%)	-0.38 (5.7%)	1.9	3.9	6.1

[7] For a more complete description of all the studies evaluated the reader is directed to Sections 5 and 6 of the MCLG Approaches Report. For a discussion on the uncertainties related to the approach the reader is directed specifically to section 6.5.

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Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 3% Decrease in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a,b,c]			Dose of Perchlorate per 1% to 3% Decrease in Endpoint (µg/kg/day)[a,b,c]		
				1%	2%	3%	1%	2%	3%
Korevaar et al., (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 (3.1%)	-0.41 (6.2%)	-0.61 (9.2%)	3.1	6.7	10.8
Pop et al., (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 (1.0%)	-0.19 (2.8%)	-0.28 (4.2%)	1.3	2.8	4.3
Pop et al., (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 (0.9%)	-0.16 (2.4%)	-0.23 (3.5%)	1.1	2.3	3.5
Pop et al., (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 (0.6%)	-0.12 (1.8%)	-0.18 (2.6%)	0.8	1.7	2.6
Endendijk et al., (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 (0.45%)	-0.08 (1.2%)	-0.12 (1.9%)	0.4	1.1	1.8
Finken et al., (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 (4.2%)	-0.57 (8.5%)	-0.85[d] (12.7%)	4.4	9.8	16.5[d]

[a]. The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1%, 2%, or 3% change from the standardized mean for each test (i.e., 100 points), which equates to a 1, 2, or 3 point change, respectively. The analyses for anxiety/depression score and SD of reaction time are based on a 1%, 2%, or 3% change from the study mean of each measure, which for anxiety/depression is 0.01, 0.02, or 0.03 points, respectively, and for reaction time is 2.7, 5.4, and 8.1 milliseconds (study mean SD of reaction time = 270 ms), respectively.
[b]. This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.
[c]. The BBDR model with a pTSH of 0.398 was used for these analyses.
[d]. The value which results in a 3% change in the standard deviation of reaction time falls between 16 and 17 µg/kg/day. Because data was not available on the changes of fT4 at doses between 16 and 17 µg/kg/day perchlorate, the EPA took the midpoint of the range of values for the change in fT4 at 16 and 17 µg/kg//day and assumed the dose of perchlorate associated with this change was the midpoint between 16 and 17 µg/kg/day.

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H. Identifying a Point of Departure for Developing the MCLG

From the seven analyses presented in Table III-2 above, the EPA chose to use its independent analysis of the Korevaar et al., (2016) data (comprising of 3,600 useable mother/child data pairs) as the basis for calculating the point of departure (POD) for the MCLG. There are three reasons for this selection: 1) there is sufficient quantitative data to derive a health impact function for the sensitive population of interest; 2) the analysis adjusts for an appropriate set of confounders, and 3) the neurodevelopmental endpoint – intelligence quotient (IQ) – is more straightforward to interpret because there is more national and cross-national data available (more on the selection of this endpoint below). The other studies presented in Table III-2 do not provide one or more of these features (USEPA, 2018b).

The five identified papers evaluated a variety of endpoints with Korevaar et al., (2016) evaluating IQ, Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) using the Bayley Scale to evaluate PDI and MDI, Finken, van Eijsden, Loomans, Vrijkotte, and Rotteveel (2013) evaluating the SD of reaction time, and Endendijk, Wijnen, Pop, and van Baar (2017) evaluating anxiety/depression scores using the Child Behavioral Check List (CBCL). The SD of reaction time from Finken et al., (2013) was not well-received by the peer reviewers (External Peer Review for U.S. EPA, 2018) because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al., (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al., (2017) nor the Finken et al., (2013) analyses had functions for the sensitive life

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stage (i.e., their analyses were based on the full range of fT4 levels and did not concentrate on the impacts of low-end fT4 levels). For these reasons, the Endendijk et al., (2017) and Finken et al., (2013) papers were not selected for further evaluation.

The Korevaar et al., (2016) original and independent analyses are preferable compared to the Pop, Kuijpens, et al., (1999) and Pop, Brouwers, et al., (2003) studies because neither function derived from the Pop et al., studies was adjusted for confounders. Additionally, both Pop et al., papers have an N < 50 compared to the Korevaar et al., analyses, which have an N of greater than 3,600.[8]

Although the original Korevaar et al., (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al., (2016) EPA reanalysis was chosen over the original analysis because it included modifications to the analysis at the suggestion of the peer review panel. The revised analysis controls for a more parsimonious set of confounders (e.g., previously included variables such as infant gender, maternal parity, birthweight, mother's body mass index (BMI), and gestational age at blood draw that are not related to both the exposure and the outcome were excluded), thus decreasing the chances of overfitting the estimation of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al., (2016) model because of the feedback received during the peer review of the MCLG Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

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[8] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609 due to the exclusion of subjects with imputed values for maternal fT4.

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Korevaar et al., [2016] controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al., (2016) data, and making decisions about data quality and influential data points in the analysis. That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values. Subsequently, the EPA selected the Korevaar et al., (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ[9].

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[9] A more complete description of the EPA independent analysis of the Korevaar et al. (2016) data can be found in Section 6.3.2 of the MCLG Approaches Report.

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As indicated above, the EPA has utilized a health protective approach to this analysis consistent with the SDWA definition of the MCLG. The peer reviewers commented that this approach was fit-for-purpose. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes. The existence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes has strong support from the literature on the subject; however, not every study identified an association between maternal fT4 and the specified outcome of interest, and the state of the science on this relationship is constantly evolving. As explained earlier, the results of the EPA's dose-response literature review identified 31 studies that evaluated the association between maternal thyroid hormone levels and offspring neurodevelopment, with neurodevelopment defined using a variety of endpoints related to cognition, behavior, and other outcomes such as autism. Among these studies, only 16 were deemed to potentially possess information that could inform a dose-response relationship. The other 15 only presented data on categorical analyses assessing the impact of maternal hypothyroxinemia on the neurodevelopmental outcomes of interest. Therefore, because the data presented was only a comparison of two groups, there was not information that could be used to inform a dose-response function.

Of the 16 studies that potentially had data to inform a dose-response function, 10 evaluated cognition using a variety of tests including various IQ tests (three papers; Ghassabian et al., 2014; Korevaar et al., 2016; Moleti et al., 2016), Bayley Scales of Infant Development (two papers; Pop et al., 1999; Pop et al., 2003), and other validated tests associated with child

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cognition such as expressive language delay or test performance (five papers; Finken et al., 2013; Henrichs et al., 2010; Kastakina et al., 2006; Noten et al., 2015; Oken et al., 2009). Six of these papers found a statistically significant relationship between maternal fT4, as a continuous variable, and offspring cognitive outcome (Korevaar et al., 2016; Pop et al., 1999; Pop et al., 2003; Finken et al., 2013; Henrichs et al., 2010, Kastakina et al., 2006). However, there were studies where maternal fT4 as a continuous variable was not significantly associated with the outcome of interest. For example, in Ghassabian et al., (2014) the authors found maternal hypothyroxinemia to be associated with an average of a 4.3-point reduction in IQ in their offspring compared to offspring of non-hypothyroxinemic mothers. Nevertheless, when assessing the relationship between the continuous measure of maternal fT4 as a continuous variable (across the entire range of fT4 levels) and child IQ, the authors did not find a significant relationship. Additionally, Moleti et al., (2016) found the relationship between maternal fT4 and child IQ to be consistently inversely associated with IQ scores, but their assessment failed to reach statistical significance. This study included fewer than 60 study participants and was considered by the authors to be a pilot assessment.

In addition to the cognitive effects assessed and modeled, the EPA identified four papers that assessed maternal fT4 status and behavioral outcomes (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017), one paper that assessed maternal fT4 status and autism (Roman et al., 2013) and one paper that evaluated odds of a schizophrenia diagnosis as associated with maternal thyroid hormone status (Gyllenberg et al., 2016). From this group of papers, the majority of papers found an association either between maternal

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hypothyroxinemia or maternal fT4 as a continuous variable and the outcome of interest (Endendijk et al., 2017; Modesto et al., 2015; Oostenbroek et al., 2017; Roman et al., 2013; Gyllenberg et al., 2016). However, this was not always the case as exemplified by Ghassabian et al., (2011) and Gyllenberg et al., (2016). Although Endendijk et al., (2017) found maternal fT4 to have a significant adverse impact on anxiety/depression using the Child Behavioral Check List (CBCL), Ghassabian et al., (2011) did not find any association between maternal thyroid hormone status and offspring score on various components of the CBCL. Additionally, Gyllenberg et al., (2016) found maternal hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers. Gyllenberg et al., (2016) also found an association with odds of schizophrenia diagnosis using conditional logistic regression when assessing fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range); however, this relationship was attenuated after controlling for smoking.

Not every paper the EPA located in its literature review found a statistically significant association between maternal fT4 as a continuous variable (i.e., the initially identified 16 studies identified as potentially useful to inform a dose-response function) and the neurodevelopmental outcome of interest. However, many studies located in the EPA literature review, several meta-analyses (Fan & Wu, 2016; Thompson et al., 2018 and Wang et al., 2016), the American Thyroid Association (Alexander et al., 2017) and the U.S. EPA's SAB (2013) have concluded there is a relationship between maternal hypothyroxinemia and various neurodevelopmental outcomes.

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The relationship between maternal fT4 levels and neurodevelopmental outcomes appears strongest in the hypothyroxinemic range, and when looking at the entire range of fT4 as a continuous variable (as opposed to a categorical cut off), the significant relationship between the two variables may dissipate. Therefore, the EPA has concentrated on the neurodevelopmental impacts of changes in fT4 in the lower range of fT4 from the Korevaar et al., (2016) data. In an attempt to minimize uncertainty, the EPA reanalyzed the data collected by Korevaar et al., (2016) using a spline function that estimates a coefficient specifically for the low range of the fT4 data.

There are a variety of neurodevelopmental endpoints used to examine behavior and cognition in children (e.g., intelligence quotient (IQ), motor skills, vocabulary and language development, stimulus responsiveness, etc.). The EPA selected IQ decrements because this was the endpoint evaluated in the Korevaar et al., (2016) study. The EPA determined that the Korevaar study was the most rigorous analysis that examined the relationship between decreased thyroid hormones and neurodevelopmental effects. As such, in the derivation of the MCLG, IQ is a surrogate for a suite of potential neurodevelopmental effects that might occur to the offspring of hypothyroxinemic and iodine deficient mothers.

There are several different tests that are widely used to measure IQ in children, including the Stanford-Binet and the Wechsler Intelligence Scale for Children (WISC) (Sternberg et al., 2001). Each of these tests is intended to assess a child's global functioning and uses a numerical IQ point scale (Beres et al., 2000). IQ scores are standardized by age and sex group with a mean score of 100 points and a standard deviation of 15 (Beres et al., 2000). Although the specific

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tasks differ by test, all IQ tests contain a number of tasks to assess diverse skills (Sternberg et al., 2001). For example, the WISC test evaluates full-scale IQ using a combination of verbal and performance scales (verbal IQ and performance IQ may also be assessed separately) (Beres et al., 2000). The verbal scale includes tasks such as arithmetic, vocabulary, and comprehension, while the performance scale includes tasks such as picture completion, block design, and object assembly (Beres et al., 2000). The WISC was standardized using a sample of 2200 U.S. children aged 6 to 16 years old (Seashore et al., 1950). It has been well validated and has demonstrated high reliability, with a reliability coefficient of 0.96 observed across age groups (Beres et al., 2000).

Associations have been found between IQ scores and both educational achievement and attainment, though observed correlations vary widely. In a review of the literature, Sternberg et al., (2001) suggest that IQ scores explain approximately 25% of the variance in academic achievement. Evidence also suggests that IQ is linked to career outcomes and job performance, with observed correlations ranging from approximately 0.2 to 0.6 (Sternberg et al., 2001). Research suggests that children's rearing environment, including parental education, while growing up may increase IQ scores in adolescence by several points (e.g., Kendler et al., 2015).

IQ scores have been used to help diagnose disorders such as intellectual disability and to identify children for placement into specialized learning programs (Beres et al., 2000). For example, in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) IQ scores are used in an individual's comprehensive assessment to determine intellectual disability, which pairs standardized testing of intelligence with a clinical assessment of adaptive

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functioning. Intellectual disability is considered for individuals with an IQ score of about 70 or below (American Psychiatric Association, 2013).

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 percent extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint. Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, "[a] BMR of 1% has typically been used for quantal human data from epidemiology studies" (p. 21, USEPA, 2012).

For the specific context of setting an MCLG for perchlorate, the EPA made a policy decision to evaluate the level of perchlorate in water associated with a 1 percent decrease, a 2 percent decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points). The EPA selected IQ as a surrogate for neurodevelopmental effects based upon its evaluation of the epidemiologic literature describe above. The need to utilize the best available peer reviewed data to inform scientific assumptions and policy choices to meet the statutory requirements associated with developing an MCLG under the SDWA highlights the challenges associated with regulating chemicals for which potential effects are indirect, and scientific data

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do not address all uncertainties. The Agency must make a policy decision informed by science, consistent with statutory requirements even in situations where the data do not provide clear choices. To develop the proposed MCLG for perchlorate, the EPA made a policy decision to use a 2 IQ point decrement in the population-distribution of IQ for the sensitive population. By selecting this approach, the EPA is not establishing a precedent for future Agency actions on other contaminants for which there is concern about potential thyroid effects, either under the SDWA or other statutory frameworks.

Applying these response rates to the results from the reanalysis of Korevaar et al., (2016), results in a POD dose of 3.1 μg/kg/day for a 1 point decrease in the sensitive population's IQ, a POD dose of 6.7 μg/kg/day for a 2 point decrease in the sensitive population's IQ, and a POD dose of 10.8 μg/kg/day for a 3 point decrease in the sensitive population's IQ. These PODs associated with a 1, 2, or 3 point decrease from the standardized mean IQ are calculated for the most sensitive population. Specifically, the POD is designed to provide an adequate margin of safety for the fetuses of mothers with fT4 at the 10th percentile of a population with iodine intake of 75 μg/day and a TSH feedback loop that is less than 60% as effective as individuals with median TSH feedback loop efficacy. That is, the analysis is designed to protect the population of fetuses of mothers with suboptimal thyroid functioning. For these reasons, and for the methodological reasons described previously, the EPA believes that the selection of these parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive population and allows for an adequate margin of safety.

I. Translate PODs to RfDs

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When deriving an RfD the EPA evaluates whether to apply uncertainty/variability factors to account for heterogeneity of effect in the target population and data gaps (USEPA, 2002). As presented in *A Review of the RfD & RfC Processes* (USEPA, 2002) the EPA considers the following uncertainty factors: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a no-observed-adverse-effect-level (NOAEL), and an incomplete database. The factors are intended to account for: 1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); 2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); 3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); 4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and 5) uncertainty associated with extrapolation when the database is incomplete. (U.S. EPA, 2011b) The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

The EPA considered variation and uncertainty in the relationship between exposure and response among the members of the human population (i.e., uncertainty factor (UF) for within-human variability/ inter-individual variability, UF_H). For this analysis a UF of 3 is used. The approach taken to derive the RfD attempts to address variability between the general population and the sensitive population. Specifically, the EPA was able to modify the strength of the TSH feedback loop and iodine intake levels in the BBDR model and concentrate on the dose-response relationship between lower level (as opposed to median level) fT4 and neurodevelopmental

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outcomes. However, there is still uncertainty in the relationship between perchlorate exposure and subsequent neurodevelopmental outcomes[10]. There are very few toxicokinetic calibration data available for the perchlorate to thyroid hormone relationship described in the BBDR model. On the toxicodynamic side of the BBDR model, aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. There are also uncertainties linking maternal fT4 levels to offspring IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S. based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.

Further, as discussed in section III.C. of this notice the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neuorodevelopmental outcomes. In addition, this analysis is assuming that protecting a first trimester fetus from alterations in maternal fT4 will protect the fetus throughout pregnancy. This is based on epidemiologic evidence that shows the relationship between first trimester maternal fT4 and neurodevelopmental outcomes. This is potentially

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[10] For a more complete discussion on the uncertainties in the analysis the reader is directed to Sections 3.5 and 6.5 of the MCLG Approaches Report.

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because before mid-gestation, the mother is the only source of thyroid hormone for the fetus (Morreale de Escobar et al., 2004). Therefore, when evaluating maternal fT4 as associated with neurodevelopmental outcomes it is critical to understand the first-trimester levels. Later in gestation, when the fetal thyroid begins secreting thyroid hormones, maternal fT4 may no longer be a good surrogate for the thyroid hormone levels available to the fetus. Given that the fetal thyroid has had little time to develop, its iodine storage is much less than that of an adult, hence there may be more sensitivity to short-term fluctuations in iodine availability and uptake that may have little impact on maternal levels. Therefore, there is some uncertainty about the impact perchlorate may have on the fetal thyroid gland, and subsequent neurodevelopmental impacts, in later trimesters of pregnancy. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones (Savin, Cvejić, Nedić, & Radosavljević, 2003; van Den Hove, Beckers, Devlieger, De Zegher, & De Nayer, 1999), so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and perchlorate exposure. Therefore, as described above, the EPA selected an intraspecies UF of 3 to account for the uncertainties in modeling the impacts of perchlorate ingestion on the thyroid hormone levels for pregnant mothers with low iodide intake, and the uncertainties in predicting the neurodevelopmental effects of these thyroid hormone changes on their children.

The EPA considered but did not derive a Data-Dependent Extrapolation Factor (DDEF) for this analysis. As described above, the UFs are applied based on the uncertainties in the

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perchlorate to thyroid hormone and thyroid hormone to neurodevelopment relationship[11]. As noted above, the Agency has opted to apply a UF of 3 to the POD, which adds an adequate margin of safety to the MCLG derivation. Section 4.4.5.3 (p 4-42) of *A Review of the RfD & RfC Processes* recommends reducing the intraspecies UF from a default of 10 "only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s)" (p. xviii, USEPA, 2002).The EPA selected a UF of 3 instead of the full 10 because the modeled groups within the population that are identified as likely to be at greater risk to perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother) and has selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake).

Below we list the other uncertainty factors added and the justification.

- Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A). For this analysis an UF of 1 is used because this factor is not applicable since animal studies were not used to develop the BBDR model nor were they used to relate alterations in maternal fT4 to IQ.
- Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, UF_S). An uncertainty factor of 1 is used. Extrapolating from subchronic to chronic exposures did not occur as the BBDR model was designed to assess long-term steady-state conditions in the

[11]As explained in U.S. EPA, 2014 "UFs incorporate both extrapolation components that address variability (heterogeneity between species or within a population) and components that address uncertainty (i.e., lack of knowledge)...whereas DDEFs focus on variability" (p. 7, US EPA, 2014).

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non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations.

- Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L). A more sophisticated BBDR modeling approach, coupled with extrapolation to changes in IQ using linear regression, was used to determine a POD that would not be expected to represent an adverse effect. Subsequently an uncertainty factor of 1 is used. LOAELs and NOAELs were not identified or used in this approach.
- Uncertainty factor for database deficiency to address the potential for deriving an inadequately protective RfD in the instance where the available database provides an incomplete characterization of the chemical's toxicity (database deficiency, UF_D; USEPA, 2002). An uncertainty factor of 1 is used as "[t]he mode of action of perchlorate toxicity is well understood" (SAB for the U.S. EPA, 2013, p. 2).
- The product of all the uncertainty factors (UF_H) is 3 (3 x 1 x 1 x 1 x 1).

Below we generate RfD's for each of the points of departure.

Using the POD of 6.7 μg/kg/day based on a 2 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive a RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.2\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 3.1 μg/kg/day based on a 1 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

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$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.0\ \frac{\mu g/kg}{day}$$

Using an alternative POD of 10.8 µg/kg/day based on a 3 percent decrease in the population standardized mean IQ from the EPA's independent analysis of the Korevaar et al., (2016) data, the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{10.8}{3} = 3.6\ \frac{\mu g/kg}{day}$$

J. Translate RfD into an MCLG

To translate the RfD (µg/kg/day) to a concentration in drinking water (µg/L), the EPA used the following equation:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate in micrograms per liter (µg/L);

RfD = reference dose (1.03 µg/kg/day for a 1 percent decrease in IQ, 2.23 µg/kg/day for a 2 percent decrease in IQ, or 3.6 µg/kg/day for a 3 percent decrease in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution of drinking water to overall perchlorate exposure.

To calculate the MCLGs, the EPA selected the 90th percentile body-weight adjusted drinking water ingestion rate specific to women of childbearing age (i.e., non-pregnant, non-lactating, 15–44 years of age (0.032 L/kg/day). This decision is consistent with the analysis used in deriving an RSC, which was performed using food consumption information for a population of women of childbearing age from NHANES. The 90th percentile is chosen to account for

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variability in drinking water ingestion rates, but also adds another layer of health protection for 90% of women (Table III-3).

The EPA did not use water intake data for pregnant women because the sample sizes were too small to be statistically stable. The use of the drinking water intake for 15-44 year old women is consistent with the analysis used in deriving an RSC_W (described below), which was performed using food consumption information for a population of women of childbearing age from NHANES. The EPA acknowledges there is a difference in the age range defining women of childbearing age used to develop the drinking water ingestion rate and that used to develop the RSC (20 – 44 years of age). The age range used to develop the RSC was based on the range of ages used to define women of childbearing age in developing the BBDR model. However, the EPA's Exposure Factors Handbook (USEPA, 2011c) identifies drinking water ingestion rates for women 15-44 years of age as corresponding to women of childbearing age.

The age range used for women of childbearing age in the BBDR model fits within the age range used to develop the ingestion rates provided in the Exposure Factors Handbook. Thus, the Agency believes the difference in the age ranges will have minimal impact on the resulting MCLG analysis.

Table III-3. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant	65	0.014[a]	0.033[a]	0.043[a]
Lactating	33	0.026[a]	0.054[a]	0.055[a]
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

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Female Population Categories	Sample Size	Mean	90th Percentile	95th Percentile
[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, 1994-1996 (FASEB/LSRO, 1995).				

Individuals are exposed to perchlorate through ingestion of both food and drinking water (ATSDR 2008, Huber et al., 2011). In calculating the MCLGs, the EPA applies a relative source contribution (RSC) to the RfD to account for the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate have been considered. Thus, the RSC for drinking water is based on the following equation where "Food" is the perchlorate dose from food ingestion:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

To estimate the dose of perchlorate for women of childbearing age coming from food, the EPA implemented a data integration methodology that combined demographic variables, food consumption estimates, and perchlorate contamination estimates in food from multiple sources (USEPA, 2019c). These sources include:

- The NHANES data available from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) including the What We Eat in America (WWEIA) 24-hour food diary data (CDC & NCHS, 2007, 2009, 2011); and
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) (U.S. Food and Drug Administration (FDA), 2015), which analyzes contaminants in about 280 kinds of food and beverages commonly consumed by the U.S. population.

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The NHANES data provided individual food consumption profiles for female participants age 20-44 (the women of childbearing age range used for the BBDR model). The EPA matched TDS perchlorate concentrations with each food consumed by a participant and calculated each participant's daily perchlorate dose (μg/kg/day) from food using the participant's body weight. The EPA estimated each participant's perchlorate dose using both mean and 95th percentile perchlorate concentrations in food. The details of these assumptions are explained on page 5-5 of the Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (USEPA 2019c). Specifically, the EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the 20 samples included in the TDS data. In order to estimate the 95th percentile from the 20 samples, the EPA used the second-highest test result for each food to represent the 95th percentile concentration. While simple, this method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine (Carriquiry et al., 2016). The aforementioned method for identifying the 95th percentile concentration of perchlorate from food was selected over other, more "statistically based" methods for estimating percentiles as it avoids the need to assume a distributional shape for the samples. The EPA determined that it was more reliable to assume the empirically derived distribution as the basis for selecting the 95th percentile (i.e., assuming the distribution was equal to the distribution of samples collected in the TDS), as opposed to forcing a distributional shape, such as normal or log-normal, onto the data that may not necessarily be appropriate. With the chosen method, we can at least be sure that the distributional shape is appropriate for the data at hand, whereas by choosing the alternative that assumes a distributional

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shape, in many instances we would not even be certain of that. The EPA used these individual bodyweight-adjusted perchlorate doses from food to calculate distributions of perchlorate dose from food for the population of women age 20-44.

Table III-4 presents the mean and selected percentiles of the distribution of perchlorate dose from food for women ages 20-44, for both mean and 95th percentile perchlorate concentrations in food based on the TDS. To calculate the RSC, the EPA selected the 90th percentile dose of perchlorate from food, assuming a scenario where the food contained the 95th percentile perchlorate concentration. This corresponds to a perchlorate dose for food of 0.45 μg/kg/day. The EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile perchlorate food concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

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Table III-4. Perchlorate Dose from Food (µg/kg/day) in U.S. Women Ages 20-44 using the mean and 95th Percentile TDS Results[1]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose from Food (µg/kg/day)	
	Based on Mean Concentrations of Perchlorate in Food	Based on 95th Percentile Concentrations of Perchlorate in Food
Mean	0.09 – 0.12	0.23 – 0.24
50th Percentile	0.08 – 0.10	0.17 – 0.19
90th Percentile	0.18 – 0.21	**0.45**
99th Percentile	0.33 – 0.38	1.16 – 1.17

[1] Ranges are due to various approaches for handling values <level of detection. If no range is presented all approaches resulted in the same value.
Bolded value represents the selected value

The EPA used the drinking water intake and perchlorate dose from food to calculate MCLGs for the three RfD values. Table III-5 shows the RSC values for the three RfD values and the corresponding MCLGs calculated using the EPA's standard equation.

Table III-5. Estimates for RSC and MCLG by RfD

RfD[a] (µg/kg/day)	RSC_W[b] (percent)	DWI (L/kg/day)	MCLG[c] (µg/L)
1.0	56%	0.032	18
2.2	80%	0.032	56
3.6	80%[d]	0.032	90

a. The RfD values corresponding to protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (i.e., TSH feedback is reduced to be approximately 60 percent less effective than for the median individual) from either a 1-point IQ loss, 2-point IQ loss, or a 3-point IQ loss, respectively.

b. The EPA calculated RSC values based on the following equation given a Food intake of 0.45 µg/kg/day:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

c. The EPA calculated the MCLG values based on the following equation given the respective RfD and RSC values and the DWI:

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$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

d. The calculated RSC value using the equation in footnote b is 88 percent. However, the EPA has opted to follow previously established recommendations which employs a ceiling of 80 percent for the RSC value (USEPA 2000d).

IV. Maximum Contaminant Level Goal and Alternatives

Section 1412(a)(3) of the SDWA requires the EPA to propose a maximum contaminant level goal (MCLG) simultaneously with the NPDWR. The MCLG is defined in Section 1412(b)(4)(A) as "the level at which no known or anticipated adverse effects on the health of persons occurs and which allows an adequate margin of safety." The EPA is proposing an MCLG of 56 μg/L based on the rationale and methodology described in Section III above. The derivation of the proposed MCLG uses a point of departure based upon a two percent decrease in IQ for offspring of hypothyroxinemic women of child bearing age have with low iodine intake. The EPA selected a 2 percent decrease in IQ for the proposed perchlorate MCLG because this represents a small change in IQ, well below one standard deviation for the subpopulation of interest.

As described in Section III, the EPA has selected model parameters and other factors for the derivation of the MCLG that are health protective, including the focus on the most sensitive life stage. The EPA believes that the selection of the combination of protective parameters and this point of departure assures no known or anticipated adverse effects on the health of the most sensitive subpopulation and allows for an adequate margin of safety. The EPA also acknowledges the uncertainties in the derivation of the proposed (and alternative) MCLGs. The EPA acknowledges in particular the challenge associated with selecting the decrement of IQ that

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represents an adverse effect at the population level and the uncertainties in predicting the dose of perchlorate that may result in a particular IQ decrement given the absence of robust human epidemiological data directly linking perchlorate exposure to IQ decrements. The Agency seeks comment on the alternative MCLG values of 18 μg/L and 90 μg/L, which the EPA derived using the methodology described in Section III based on a one percent and three percent decrease in IQ, respectively.

V. Maximum Contaminant Level and Alternatives

Under section 1412(b)(4)(B) of the SDWA, the EPA must establish a maximum contaminant level (MCL) as close to the MCLG as is feasible. The EPA evaluated available analytical methods to determine the lowest concentration at which perchlorate can be measured and evaluated the treatment technologies for perchlorate that have been examined under field conditions (USEPA 2018a, 2019b). The EPA determined that setting an MCL equal to the proposed MCLG of 56 μg/L is feasible given that the approved analytical method for perchlorate for UCMR 1 has a minimum reporting level (MRL) of 4 μg/L (USEPA 1999, 2000c) and that available treatment technologies can treat to concentrations well below 56 μg/L (USEPA, 2018c). Therefore, the EPA is proposing to set the MCL for perchlorate at 56 μg/L.

Because the EPA is taking comment on alternative MCLG values of 18 μg/L and 90 μg/L the Agency evaluated the feasibility of setting an MCL at these levels. The EPA determined that the proposed MCL of 56 μg/L is feasible, therefore a higher MCL alternative such as 90 μg/L is also feasible. The EPA has concluded that analytical methods are capable of measuring perchlorate at 18 μg/L and that treatment technologies have been demonstrated to achieve this

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level under field conditions (USEPA 2018a, 2019b). Therefore, the EPA is requesting comment on the feasibility of the proposed MCL of 56 µg/L as well as the feasibility of the alternative MCLs of 18 µg/L and 90 µg/L.

As the occurrence analysis in section VI demonstrates, there is infrequent occurrence of perchlorate at 18 µg/L, 56 µg/L, or 90 µg/L. Therefore, the EPA did not evaluate alternative MCL values greater than the corresponding MCLG values. The purpose for evaluating alternative MCL values is to determine whether there is an MCL at which benefits justify the costs of setting an MCL. Given infrequent occurrence, the majority of the costs associated with establishing an NPDWR for perchlorate are for administrative and initial monitoring activities (see section XI.B), which will not be significantly affected by MCL values greater than corresponding MCLG values.

When proposing an MCL, the EPA must publish, and seek public comment on, the health risk reduction and cost analyses (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)), including: the quantifiable and nonquantifiable health risk reduction benefits attributable to MCL compliance; the quantifiable and nonquantifiable health risk reduction benefits of reduced exposure to co-occurring contaminants attributable to MCL compliance; the quantifiable and nonquantifiable costs of MCL compliance; the incremental costs and benefits of each alternative MCL; the effects of the contaminant on the general population and sensitive subpopulations likely to be at greater risk of exposure; any adverse health risks posed by compliance; and other factors such as data quality and uncertainty. The EPA provides this information in section XII. The EPA must base its action on the best available, peer-reviewed

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science and supporting studies, taking into consideration the quality of the information and the uncertainties in the benefit-cost analysis (SDWA Section 1412(b)(3)). The following sections, as well as the health effects discussion in section III document the science and studies that the EPA relied upon to develop estimates of benefits and costs and understand the impact of uncertainty on the Agency's analysis.

VI. Occurrence

The UCMR 1 is the primary source of occurrence data the EPA relied on to estimate the number of water systems (and associated population) expected to be exposed at levels of perchlorate which could potentially exceed the proposed and alternative MCL levels. Since UCMR 1 data was first used to inform the Agency actions on the 2008 preliminary regulatory determination and the 2011 final regulatory determination, the Agency has modified its analysis of the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions at some States that have enacted perchlorate regulations since the UCMR 1 data was collected. Despite these updates, the EPA continues to rely on the UCMR 1 data because they are the best available data collected in accordance with accepted methods from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

In 1999, the EPA developed the first round of the UCMR program in accordance with SDWA requirements to provide national occurrence information on unregulated contaminants

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(USEPA, 1999, 2000b). The UCMR 1 required sampling from systems in all 50 States, the District of Columbia, four U.S. territories, and tribal lands in five EPA Regions including:

- all 3,097 large (serving more than 10,000 people) CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources), or two samples collected 5 to 7 months apart (ground water sources); and
- a statistically representative selection of 800 small CWSs and NTNCWSs, which analyzed either four quarterly samples collected at 3-month intervals (surface water sources) or two samples collected 5 to 7 months apart (ground water sources).

Water systems submitted UCMR 1 sampling results to the EPA from 2001 until 2005. Water systems were required to analyze samples for 26 contaminants including perchlorate. The EPA established a minimum reporting level of 4 μg/L for perchlorate in the UCMR.

The EPA conducted a data quality review of the UCMR 1 data submitted by systems prior to analyzing the occurrence data for the 2011 perchlorate regulatory determination. The UCMR 1 dataset used by the EPA included 34,331 samples with 637 measurements of perchlorate above the minimum reporting level from 3,865 systems.

In September of 2012, the EPA received a "Request for Correction" letter from the United States Chamber of Commerce regarding information and data (i.e., the occurrence of perchlorate in drinking water) used by the EPA in its 2011 determination to regulate perchlorate. The U.S. Chamber of Commerce letter stated that the EPA relied upon: 1) data that did not comply with data quality guidelines and 2) data that was not representative of current conditions.

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In response[12] to the U.S. Chamber of Commerce, the EPA conducted a detailed assessment of the source water sample detections and determined that it was most appropriate to exclude the source water sample detections from the UCMR 1 perchlorate data set when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 perchlorate data set. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 perchlorate data set. As a result of the assessment, the EPA removed 199 source water samples (97 detections) that could be paired with a second follow-up sample located at the entry point to the distribution system. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections from 149 PWSs.

Table VI-1 shows sample distribution by system size category and measurement status. It also shows the number of entry points and systems where perchlorate measurements were reported. The entry point estimates differ from the system estimates because many water systems have more than one entry point. For example, a ground water system with two wells that has separate connections to the distribution system has two entry points.

In response to the U.S. Chamber of Commerce request, the EPA has also reassessed the UCMR 1 data in light of the adoption of regulatory limits in two states. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 (MassDEP, 2006), and California promulgated a drinking water standard of 6 μg/L in 2007 (California Department of

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[12] See the EPA response letter at https://www.epa.gov/sites/production/files/2017-08/documents/12004-response_0.pdf

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Public Health, 2007). Systems in these states are now required to keep perchlorate levels in drinking water below their state limits, which are lower than the proposed MCL and alternative MCLs. Therefore, the UCMR 1 sampling results from systems in these states do not reflect the current occurrence and exposure conditions. For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that no additional monitoring and treatment costs would be incurred by the systems in the States of California and Massachusetts. Systems in California account for some of the perchlorate measurements reported below. The notes in the tables below indicate whether results include or exclude systems in California and Massachusetts.

To update the occurrence data for systems sampled during UCMR 1 from the States of California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

Out of the 540 detections previously described the EPA updated data for 321 detections (320 from California systems and 1 from a Massachusetts system). The convention used by the EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported compliance monitoring data, if more than one

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data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were the EPA could not find updated entry point data, then the original data from UCMR 1 for such entry point was kept.

Table VI-1. UCMR 1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
Sample measurements ≥ 4 μg/L	15	525	540
Sample measurements > 18 μg/L	1	16	17
Sample measurements > 56 μg/L	0	2	2
Sample measurements > 90 μg/L	0	1	1
Total entry points	1,454	13,482	14,936
Entry points at which measurements ≥ 4 μg/L	8	328	336
Entry points at which measurements > 18 μg/L	1	16	17
Entry points at which measurements > 56 μg/L	0	2	2
Entry points at which measurements > 90 μg/L	0	1	1
Total systems	797	3,068	3,865
Systems at which measurements ≥ 4 μg/L	8	141	149
Systems at which measurements > 18 μg/L	1	14	15
Systems at which measurements > 56 μg/L	0	2	2
Systems at which measurements > 90 μg/L	0	1	1

Source: (USEPA, 2019b). The total row counts and counts of measurements ≥ 4 μg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 537 systems in total and 51 systems at which measurements ≥4 μg/L. The instances where perchlorate measurements equal or exceed either 18 μg/L, 56μg/L, or 90 μg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 μg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

Table VI-2 shows the service populations that correspond with the occurrence summary in Table VI-1. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

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Table VI-2. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
Population served by entry points at which measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Population served by entry points at which measurements > 18 µg/L	2,155	618,406	620,560
Population served by entry points at which measurements > 56 µg/L	0	32,432	32,432
Population served by entry points at which measurements > 90 µg/L	0	25,972	25,972
Total system population	2,760,570	222,853,101	225,613,671
Population served by systems at which measurements ≥ 4 µg/L	13,483	16,159,082	16,172,565
Population served by systems at which measurements >18 µg/L	4,309	696,871	701,180
Population served by systems at which measurements > 56 µg/L	0	64,733	64,733
Population served by systems at which measurements > 90 µg/L	0	25,972	25,972

Source: (USEPA, 2019b). The populations for entry points/systems with measurements ≥ 4 µg/L identify all instances where perchlorate was detected at or above the minimum reporting level, including water systems in California and Massachusetts, which account for 39.6 million of the 225.6 million total population in UCMR 1, and 1.9 million of the 4.3 million population served by entry points at which measurements ≥4 µg/L. The instances where perchlorate measurements equal or exceed either 18 µg/L, 56µg/L, or 90 µg/L exclude results from California and Massachusetts because water systems in these States must meet limits below 18 µg/L. The small system counts reflect sample results that have not been extrapolated to small systems nationwide.

As shown in the tables, 149 systems serving 16.2 million people had measured levels of perchlorate greater than the minimum reporting level. However, many of these systems have several entry points with no measured levels of perchlorate greater than the minimum reporting level; at the entry point level, the exposed population is approximately 4.3 million people served by 336 entry points. Because the uniform population distribution assumption may over or underestimate the service population of any particular entry point, the entry point estimates are uncertain. The system population estimates serve as upper bounds on exposure.

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The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the proposed MCL and alternative MCLs. The maximum measurements indicate perchlorate levels that occurred in at least one quarterly sample among surface water systems and at least one semi-annual sample among ground water systems.

Table VI-3 through Table VI-5 show the occurrence and exposure estimates based on the 56 µg/L, 18 µg/L MCL, and 90 µg/L values, respectively. Each table provides estimates of the entry points at which the maximum perchlorate concentrations exceed the MCL value. The tables also report the system-level information for these entry points.

Table VI-3: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: (USEPA, 2019b).

Table VI-4: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 18 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: (USEPA, 2019b).

1. The values shown in the table are estimates based on the UCMR 1 data. The EPA also applied the statistical sampling weights to the results to extrapolate results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

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Table VI-5: Estimated Perchlorate Occurrence and Exposure: Entry Point Max Exceeds 90 µg/L

Affected Entity	Small Systems[1]	Large Systems	Total Systems
Entry points	0	1	1
Population served	0	25,972	25,972
Water systems	0	1	1
Population served	0	25,972	25,972

Source: (USEPA, 2019b).

In summary, the perchlorate occurrence information suggests that at an MCL of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. One of these two systems would exceed the alternative MCL of 90 µg/L. In addition, at an MCL of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold.

VII. Analytical Methods

The SDWA directs the EPA to set a contaminant's MCL as close to its MCLG as is "feasible", the definition of which includes an evaluation of the feasibility of performing chemical analysis of the contaminant at standard drinking water laboratories. Specifically, the SDWA directs the EPA to determine that it is economically and technologically feasible to ascertain the level of the contaminant being regulated in water in public water systems (Section 1401(1)(C)(i)). NPDWRs are also to contain "criteria and procedures to assure a supply of drinking water which dependably complies with such [MCLs]; including accepted methods for quality control and testing procedures to insure compliance with such levels." (Section 1401(1)(D)).

To comply with these requirements, the EPA considers method performance under relevant laboratory conditions, their likely prevalence in certified drinking water laboratories,

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and the associated analytical costs. The EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water that meet these criteria. The proposed EPA methods for perchlorate are: 314.0, 314.1, 314.2, 331.0, and 332.0. A detailed description of these methods is presented in the Perchlorate Occurrence and Monitoring Report (USEPA, 2019b).

The EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent the EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, including: detection limits; instrument calibration; precision and analyte recovery; analyte retention times; evaluation of blanks; development of Quality Control acceptance criteria; analysis of field samples; and other technical aspects of sample analysis and data reporting. All of the proposed EPA analytical methods provide performance data to demonstrate their capability to reliably and consistently measure perchlorate in drinking water at the proposed and alternate MCLs.

VIII. Monitoring and Compliance Requirements

A. What are the Proposed Monitoring Requirements?

The EPA is proposing to require CWS and NTNCWSs to monitor for perchlorate in accordance with the standardized monitoring framework set out in 40 CFR 141 Subpart C (Standardized Monitoring Framework). Public water systems must sample entry points to the distribution system consistent with requirements in 40 CFR 141.23(a).

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Under the Standardized Monitoring Framework, the monitoring frequency for a public water system is dependent on previous monitoring results and whether a monitoring waiver has been granted. The EPA is proposing that consistent with the standardized monitoring framework water systems would be initially required to monitor quarterly for perchlorate. The EPA is also proposing that based upon the monitoring results States would be able to reduce the monitoring frequency to annually, once every three years or once every nine years if the State concludes that the system is reliably and consistently below the MCL. If a water system exceeds the perchlorate MCL, the system is in violation and triggered into quarterly monitoring for that sampling point in the next quarter after the violation occurred (40 CFR 141.23(c)(7)). The state may allow the system to return to the reduced monitoring frequency when the state determines that the system is reliably and consistently below the MCL. However, the state cannot make a determination that the system is reliably and consistently below the MCL until a minimum of 2 consecutive ground water or 4 consecutive surface water samples below the MCL have been collected (40 CFR 141.23(c)(8)). All systems must comply with the sampling requirements, unless a waiver has been granted in writing by the state (40 CFR 141.23(c)(6)).

B. Can States Grant Monitoring Waivers?

Under this proposal, water systems may apply to the state, and states may grant, a 9-year monitoring waiver for perchlorate if the conditions described in 40 CFR 141.23(c)(3)-(6) are met. A state may grant a waiver for surface water systems after three rounds of annual monitoring with results less than the MCL and for groundwater systems after conducting three rounds of monitoring with results less than the MCL. One sample must be collected during the

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nine-year compliance cycle that the waiver is effective, and the waiver must be renewed every nine years.

C. How are System MCL Violations Determined?

Under this proposal, violations of the perchlorate MCL would be determined in a manner consistent with 40 CFR 141.23(i)(3). Compliance with the perchlorate MCL would be determined based on one sample if the level is below the MCL. If the level of perchlorate exceeds the MCL at any entry point in the initial sample, a confirmation sample is required within two weeks of the system's receipt of notification of the analytical result of the first sample, in accordance with 141.23(f)(1). Compliance shall be determined based on the average of the initial and confirmation samples.

D. When Must Systems Complete Initial Monitoring?

Pursuant to Section 1412(b)(10), this rule would be effective three years after promulgation. To satisfy initial monitoring requirements, CWS serving populations greater than 10,000 persons must collect 4 quarterly samples for perchlorate during the second compliance period of the fourth compliance cycle (January 1, 2023– December 31, 2025) of the Standardized Monitoring Framework. NTNCWS and CWSs serving 10,000 persons or less must collect 4 quarterly samples during the third compliance period of the fourth compliance cycle (January 1, 2026 – December 31, 2028) of the Standardized Monitoring Framework.

E. Can Systems use Grandfathered Data to Satisfy the Initial Monitoring Requirements?

As proposed today, systems would be allowed to use grandfathered perchlorate data collected after January 1, 2020, to satisfy the initial monitoring requirements. To satisfy initial

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perchlorate monitoring requirements, a system with appropriate historical monitoring data for each entry point to the distribution system could use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for CWSs serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for NTNCWs and for CWSs serving 10,000 or fewer persons.

IX. Safe Drinking Water Act Right to Know Requirements

A. What are the Consumer Confidence Report Requirements?

A community water system must prepare and deliver to its customers an annual Consumer Confidence Report (CCR) in accordance with requirements in 40 CFR 141 Subpart O. A CCR provides customers with information about their local drinking water quality as well as information regarding the water system compliance with drinking water regulations. Under this proposal CWSs would be required to report perchlorate information in their CCR.

B. What are the Public Notification Requirements?

All public water systems must give the public notice for all violations of NPDWRs and for other situations. Under this proposal, violations of the perchlorate MCL would be designated as Tier 1 and as such, public water systems would be required to comply with 40 CFR 141.202. As described in Section III of this proposal, fetuses of first trimester pregnant women with low iodine are the most sensitive subpopulation, therefore, per 40 CFR 141.202(b)(1), notification of an MCL violation should be provided as soon as practicable but no later than 24 hours after the system learns of the violation under this proposal.

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X. Treatment Technologies

Systems that exceed the perchlorate MCL will need to adopt new treatment or another strategy to reduce perchlorate to a level that meets the MCL. When the EPA establishes an MCL for a drinking water contaminant, Section 1412(b)(4)(E) of the SDWA requires that the Agency "list the technology, treatment techniques, and other means which the Administrator finds to be feasible for purposes of meeting [the MCL]," which are referred to as best available technologies (BAT). These BATs are used by states to establish conditions for source water variances under Section 1415(a). Furthermore, Section 1412(b)(4)(E)(ii) requires that the Agency identify small system compliance technologies (SSCT), which are affordable treatment technologies, or other means that can achieve compliance with the MCL (or treatment technique, where applicable). The lack of an affordable SSCT for a contaminant triggers certain additional procedures which can result in states issuing small system variances under Section 1412(e) of the SDWA.

The Agency solicits public comment on the choice of available treatment technologies discussed in this section.

A. What are the Best Available Technologies?

The Agency identifies the best available technologies (BAT) as those meeting the following criteria: (1) the capability of a high removal efficiency; (2) a history of full-scale operation; (3) general geographic applicability; (4) reasonable cost based on large and metropolitan water systems; (5) reasonable service life; (6) compatibility with other water treatment processes; and (7) the ability to bring all of the water in a system into compliance. The

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Agency is proposing the following technologies as BAT for removal of perchlorate from drinking water based its review of the treatment and cost literature (USEPA, 2018a):

- ion exchange;
- biological treatment; and
- centralized reverse osmosis.

There are also non-treatment options that might be used for compliance in lieu of installing and operating treatment technologies. These include blending existing water sources, replacing a perchlorate-contaminated source of drinking water with a new source (e.g., a new well), and purchasing compliant water from another system. Below are brief descriptions of each proposed BAT.

Ion Exchange.

Ion exchange is a physical and chemical separation process that can achieve high perchlorate removal rates. Feed water passes through a vessel containing a bed of resin made of synthetic beads or gel. As feed water moves through the resin, an ionic contaminant such as perchlorate exchanges for an ion (typically chloride) on the resin. Demonstrated removal efficiencies for perchlorate are typically in the high 90 percent range and can achieve concentrations less than 4 μg/L in treated water (Drago & Leserman, 2011; Membrane Technology, 2006; Siemens Water Technologies, 2009; The Interstate Technology & Regulatory Council (ITRC) Team, 2008). The operation continues until enough of the resin's available ion exchange sites have ions from the feed water and the resin no longer effectively removes the target contaminant, i.e., the contaminant "breaks through" the treatment process. At this point,

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the resin must be disposed and replaced or regenerated. The length of time until resin must be replaced or regenerated is known as bed life and is a critical factor in the cost effectiveness of ion exchange as a treatment technology. One measurement of bed life is the volume of water that can be treated before breakthrough – called bed volumes – the number of times the resin bed can be filled before breakthrough. Several factors affect bed life, including the presence of competing ions such as nitrate and the type of resin used. Resin types tested for perchlorate removal include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective. Based on studies of the effect of competing ions on performance, perchlorate-selective resins can achieve bed lives ranging from 105,000 to 170,000 bed volumes (Blute, Seidel, McGuire, Qin, & Byerrum, 2006; Russell, Qin, Blute, McGuire, & Williams, 2008; Wu & Blute, 2010).

Perchlorate-selective resin cannot be easily regenerated for reuse; the exhausted resin must be disposed (i.e., operated on a 'throw-away' basis). This mode of operation, however, avoids the production of liquid residuals in the form of spent regenerant. Therefore, in combination with the long bed life, single-use perchlorate-selective ion exchange can be a cost-effective treatment option in spite of the need to dispose of the perchlorate-contaminated resin. Build-up of arsenic or uranium on the resin may affect waste disposal options, although studies of perchlorate-selective resins show that arsenic concentrations remain below regulatory limits for hazardous waste disposal and uranium concentrations generally remain below those that require special handling as radioactive waste (Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010). Ion exchange can increase the corrosivity of treated water (Berlien, 2003; Betts,

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1998; USEPA, 2005b) because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Such instances can be addressed by adding or adjusting corrosion control.

Biological Treatment.

Biological treatment uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment can destroy the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Removal effectiveness exceeds 90 percent for bench-scale tests and full-scale treatment plant studies (Kotlarz, Upadhyaya, Togna, & Raskin, 2016; Upadhyaya, Kotlarz, Togna, & Raskin, 2015; U.S. Department of Defense (U.S. DoD), 2008, 2009; T. D. Webster & Crowley, 2010, 2016; T. D. Webster & Litchfield, 2017). Although biological treatment is a relatively new technology for treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The California BAT specifies a fluidized bed, although studies suggest that a fixed bed is also effective. The first full-scale fluidized bed facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 (T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017). Raw water quality will affect process design, in particular, temperature affects the rate of biomass growth; at temperatures below 10 degrees Celsius, growth is inhibited and bioremediation becomes infeasible (Dugan, 2010b, 2010a; Dugan et al., 2009). This factor limits the feasibility of biological treatment in areas that experience low water temperatures during winter. In addition, bacteria in bioreactors require nutrients to grow and

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effectively reduce perchlorate. Therefore, some source waters may require supplemental addition of nutrients such as nitrogen or phosphorus (Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009).

Although the process does not produce perchlorate-contaminated wastes, periodic removal of excess biomass, e.g., through backwash, will be required. The backwash water is non-toxic and can be discharged to a sanitary sewer (U.S. Department of Defense (U.S. DoD), 2008, 2009) or recycled following clarification. Typically, post-treatment of treated water also will be required because biological treatment increases soluble microbial organic products, depletes oxygen, and can add turbidity and sulfides (Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008; T. D. Webster & Crowley, 2016; T. D. Webster & Litchfield, 2017). The treatment process, however, can result in removal of co-occurring contaminants such as nitrate (Upadhyaya et al., 2015; Webster and Crowley, 2010; Webster and Lichfield, 2017).

Reverse Osmosis.

Reverse osmosis is a membrane filtration process that physically removes perchlorate ions from drinking water. This process separates a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate or reject. This technique does not destroy the perchlorate ion and,

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therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Across multiple bench- and pilot-scale studies, reverse osmosis membranes consistently achieve perchlorate removal greater than 80 percent and up to 98 percent (Liang, Scott, Palencia, & Bruno, 1998; Nam et al., 2005; Yoon, Amy, & Yoon, 2005; Yoon, Yoon, Amy, & Her, 2005). While water quality affects process design (e.g., recovery rate, cleaning frequency, and antiscalant selection), it has relatively little effect on perchlorate removal effectiveness of reverse osmosis membranes. Reverse osmosis generates a relatively large concentrate stream, which will contain perchlorate as well as other rejected dissolved solids, which will require disposal. The large concentrate stream also means less treated water is available for distribution (e.g., 70 to 85 percent of source water), which is a disadvantage for systems with limited water supply. Because reverse osmosis can increase the corrosivity of the treated water, it may require post-treatment or blending with bypass water. Reverse osmosis can, however, remove co-occurring contaminants including arsenic and chromium-VI (Amy, Yoon, and Amy, 2005).

B. What are the Small System Compliance Technologies?

The EPA is proposing the SSCT shown in Table X-1. The table shows which of the BAT listed above are also affordable for each small system size category listed in Section 1412(b)(4)(E)(ii) of the SDWA. The Agency identified these technologies based on an analysis of treatment effectiveness and affordability (USEPA, 2018a).

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Table X-1: Proposed SSCT for Perchlorate Removal

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[a]

a. For perchlorate, the EPA has determined that implementing and maintaining this option for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

The SSCT listed in Table X-1 include a point-of-use (POU) version of reverse osmosis in addition to the ion exchange, biological treatment and reverse osmosis technologies described in the previous section. This technology can be used by small systems to comply with the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems includes a protocol that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 μg/L to a target level of 4 μg/L (NSF, 2004). Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

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The EPA identified the SSCT using the affordability criteria methodology it developed for drinking water rules (USEPA, 1998). The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5% of median household income. Table X-2 shows the expenditure margins derived for the analysis. These margins show the cap on affordable incremental annual expenditures.

Table X-2: Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a)
a. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates (U.S. Census Bureau, 2010) stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons (Bureau of Labor Statistics (BLS), 2018b).
b. Affordability threshold equals 2.5 percent of MHI.
c. Household water costs derived from 2006 Community Water System Survey (USEPA, 2009c), based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

Table X-3 shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XII.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a) and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c). Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion. Therefore, the EPA has determined that

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there are affordable small system compliance technologies available and the Agency is not proposing any variance technologies.

Table X-3: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501-3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301-10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* (USEPA, 2018a), which describes the different WBS model input assumptions that result in ranges of per-household costs shown; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.
a. For perchlorate, the EPA has determined that implementing and maintaining a POU program for systems larger than 3,300 people (greater than 1 MGD design flow) is likely to be impractical.

XI. Rule Implementation and Enforcement

A. What are the Requirements for Primacy?

This section describes the regulations and other procedures and policies primacy entities must adopt, or have in place, to implement the proposed perchlorate rule. States must continue to meet all other conditions of primacy in 40 CFR part 142. Section 1413 of the SDWA establishes requirements that primacy entities (States or Indian Tribes) must meet to maintain primary enforcement responsibility (primacy) for its public water systems. These include: (1) Adopting drinking water regulations that are no less stringent than federal NPDWRs in effect under sections 1412(a) and 1412(b) of the Act, (2) Adopting and implementing adequate procedures for enforcement, (3) Keeping records and making reports available on activities that the EPA requires by regulation, (4) Issuing variances and exemptions (if allowed by the State) under conditions no less stringent than allowed by SDWA Sections 1415 and 1416, and (5) Adopting and being capable of implementing an adequate plan for the provision of safe drinking water under emergency situations.

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40 CFR part 142 sets out the specific program implementation requirements for States to obtain primacy for the Public Water Supply Supervision Program, as authorized under section 1413 of the Act.

To implement the perchlorate rule, States would be required to adopt revisions at least as stringent as the proposed provisions in 40 CFR 141.6 (Effective Dates); 40 CFR 141.23 (Inorganic chemical sampling and analytical requirements); 40 CFR 141.51 (Maximum contaminant level goals for inorganic contaminants); 40 CFR 141.60 (Effective Dates); 40 CFR 141.62 (Maximum contaminant levels for inorganic contaminants); Appendix A to Subpart O ([Consumer Confidence Report] Regulated contaminants); Appendix A to Subpart Q (NPDWR violations and other situations requiring public notice); Appendix B to Subpart Q (Standard health effects language for public notification); and 40 CFR 142.62 (Variances and exemptions from the maximum contaminant levels for organic and inorganic contaminants). Under 40 CFR 142.12(b), all primacy States/territories/tribes would be required to submit a revised program to the EPA for approval within two years of promulgation of any final perchlorate NPDWR or could request an extension of up to two years in certain circumstances.

B. What are the State Record Keeping Requirements?

The current regulations in 40 CFR 142.14 require States with primary enforcement responsibility (i.e., primacy) to keep records of analytical results to determine compliance, system inventories, sanitary surveys, State approvals, vulnerability and waiver determinations, monitoring requirements, monitoring frequency decisions, enforcement actions, and the issuance

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of variances and exemptions. The State record keeping requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant.

C. What are the State Reporting Requirements?

Currently, States must report to the EPA information under 40 CFR 142.15 regarding violations, variances and exemptions, enforcement actions and general operations of State public water supply programs. The State reporting requirements remain unchanged and would apply to perchlorate as with any other regulated contaminant. However, the perchlorate MCL could result in a greater frequency of reporting by certain states. See discussion of Paperwork Reduction Act compliance in Section XVI for more information.

XII. Health Risk Reduction Cost Analysis

Section 1412(b)(3)(C) of the 1996 Amendments to the SDWA requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. This section addresses the HRRCA requirements as indicated:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Sections XII.C and XII.D);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Section XII.C);

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- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Section XII.B and XII.D);
- The incremental costs and benefits associated with each alternative MCL considered (Section XII.D);
- The effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sensitive populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Section XII.C and Section III);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Section XII.C); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Section XII.E).

A. Identifying Affected Entities

If the EPA issues a final NPDWR for perchlorate, it would affect the following entities: CWSs and NTNCWSs that must meet the proposed MCL and monitoring and reporting requirements; and primacy agencies that must adopt and enforce the MCL as well as the

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monitoring and reporting requirements. All of these entities would incur costs, including administrative costs, monitoring and reporting costs, and – in a limited number of cases – costs to reduce perchlorate levels in drinking water to meet the proposed MCL using treatment or nontreatment options. Section B below summarizes the method the EPA used to estimate these costs.

The systems that reduce perchlorate concentrations will reduce associated health risks. The EPA developed a method to estimate the potential benefits of reduced perchlorate exposure among the service populations of systems with elevated baseline perchlorate levels. Section C below summarizes this method used to estimate these benefits.

Section D below provides the cost and benefit estimates. The EPA prepared the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a), which is available in the docket for the proposed rule. Section XIII summarizes and discusses key uncertainties in the cost and benefit analyses.

B. Method for Estimating Costs

Some costs associated with an NPDWR are incurred by all CWS and NTNCWS (e.g. monitoring and reporting) while others are only incurred by systems with perchlorate levels exceeding the MCL. The EPA estimated costs for CWS and NTNCWS to monitor and report perchlorate levels and also estimated the costs for a subset of public water systems with perchlorate levels greater than the proposed MCL to install and operate treatment. The EPA assumed that affected water systems would adopt ion exchange treatment because it is the most cost-effective treatment option and easy to operate on a 'throw-away' basis. If site-specific

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nontreatment options are available and lower cost, then this assumption might overstate costs. The EPA also estimated the costs for States and other primacy agencies to assure systems implement the rule and to report information to the EPA.

The EPA estimated initial costs for all CWS and NTNCWS operators to read and understand the rule and provide training to their staff to implement the proposed rule. The EPA also estimated the recurring costs for all CWS and NTNCWS operators to conduct monitoring, report results, and apply for waivers. For the purpose of these estimates, the EPA assumed that both small and large systems would require the same amount of time to read the rule, apply for a waiver, and collect a water sample but that it would take large systems twice as long to provide initial training to their staff. Table XII-1 summarizes the frequency and labor hour assumptions for this analysis.

Table XII-1: Labor Hours for Drinking Water Systems Administrative and Monitoring Requirements

Activity	Frequency	Small System Hours	Large System Hours
Read the rule	one time per system	4	4
Provide initial training	one time per system	16	32
Apply to State for monitoring waiver	once every 9 years per eligible system	16	16
Collect a single finished water sample[1]	per monitoring event	1	1

Source (USEPA, 2000a). The EPA's cost analysis reflects full MCL compliance and therefore the EPA did not estimate Tier 1 notification costs.
1. The estimate is per sample. Therefore, a system conducting a year of quarterly monitoring at three entry points incurs a total of 12 hours of labor to complete the task (3 entry points x 4 samples x 1 hour per sample).

Systems will incur monitoring costs over the analysis period. The EPA estimated monitoring frequency based on the proposed initial monitoring requirements, the standard monitoring framework requirements for inorganic contaminants, and the proposed

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implementation schedule. The estimated number of monitoring samples over the analysis period shown in Table XII-2 reflect the following phases:

1. Initial monitoring; four quarterly samples at every CWS and NTNCWS entry point.

2. Preliminary regular monitoring before waiver application: three regular monitoring samples for every CWS and NTNCWS entry point (collected annually at surface water system entry points and triennially at ground water system entry points).

3. Long-term monitoring at either (a) regular monitoring frequency for entry points at systems not granted waivers (60% of surface water system and 10% of ground water systems), or (b) reduced monitoring frequency for entry points at systems receiving waivers from primacy agencies (40% of surface water systems and 90% of ground water systems), which is one sample during every nine-year compliance monitoring cycle.

Table XII-2: Estimates of Compliance Monitoring Samples by Phase and System Type, Size, and Source Water

Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
1. Initial monitoring (4 quarterly samples in one year)	All CWS and NTNCWS	92,656	370,624
2. Preliminary regular monitoring (3 annual entry point samples for surface water systems and 3 triennial entry point samples for ground water systems)	All CWS and NTNCWS	92,654	277,962
3a. Long-term monitoring, no waiver (annual entry point samples)	60% of large surface water CWS	3,324	86,424
	60% of small surface water CWS and all surface water NTNCWS	6,064	139,472
3a. Long-term monitoring, no waiver (triennial entry point samples)	10% of large ground water CWS	680	4,080
	10% of small ground water CWS and all ground water NTNCWS	7,021	35,105
3b. Long-term monitoring, waiver (1 sample every 9 years)	40% of large surface water CWS	2,216	4,432
	40% of small surface water CWS and all surface water NTNCWS	4,043	8,086

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Monitoring Phase (sampling frequency)	System Type, Size, and Source Water	Number of Entry Points[1]	Aggregate Samples[2]
3b. Long-term monitoring, waiver (1 sample every 9 years)	90% of large ground water CWS	6,117	12,234
	90% of small ground water CWS and all ground water NTNCWS	63,189	63,189

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780).

1. The EPA estimated a total of 92,656 entry points based on the total number of potentially affected systems in SDWIS/FED and the average number of entry points per system in the UCMR 1 data by size category and source water. The initial monitoring phase includes all entry points. The EPA assumed that the two entry points with MCL exceedances at the proposed MCL of 56 μg/L would continue to take quarterly samples for the duration of the analysis period, for a total of 232 samples. Thus, they are excluded from the estimates for the subsequent phases of regular and long-term monitoring. Primacy agencies may, however, allow monitoring to return to a regular schedule if treatment process operation can reliably and consistently reduce perchlorate below the MCL.

2. For Phase 3, the estimate of aggregate samples is the product of the number of entry points and the frequency of sampling during the remaining years of the analysis period. For example, large surface water CWS without a waiver conduct long-term annual monitoring for 26 years because they complete preliminary regular monitoring in year 9. In contrast, large ground water CWS without a waiver begin long-term triennial monitoring in year 16 because their preliminary regular monitoring phase lasts for 9 years (3 triennial samples) instead of 3 years (3 annual samples). The estimates also reflect schedule differences by size because large CWS begin monitoring schedules three years earlier than small CWS and all NTNCWS.

To estimate costs to CWSs and NTNCWSs associated with time spent on compliance monitoring and other administrative costs, the EPA generally uses the labor rate[13] for full-time treatment plant operators in CWSs from USEPA (2011c), which vary based on the size of the system. The EPA calculated a weighted average fully loaded hourly wage rate for water systems of $34.71.

Additionally, the EPA assumed that systems will incur an average analytical cost of $64 per sample, which is the average cost per sample obtained from multiple laboratories for perchlorate quantitation using Method 314.0.

[13] Updated to 2017$ using the BLS Employment Cost Index for Total Compensation for Private industry workers in Utilities.

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To estimate treatment cost, the EPA utilized the occurrence data described in Section VI to estimate the number of system entry points that exceed the proposed and alternative MCLs. The EPA estimated costs that those water systems would incur to install and maintain treatment using its work breakdown structure (WBS) cost estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. The WBS approach involves breaking a process down into discrete components for the purpose of estimating costs and produce a comprehensive assessment of the capital and operating requirements for a treatment system[14]. The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and nontreatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 105,000 or 170,000 bed volumes for ion exchange). The EPA used the mid-cost estimates for ion exchange to generate expected costs for all entry points requiring perchlorate removal. This technology cost-effectively removes perchlorate, but its ability to remove co-occurring contaminants depends on influent characteristics and process design. Therefore, the EPA did not assume that treatment might result in ancillary quantifiable or non-quantifiable benefits of removing co-occurring ions such as nitrate. Treatment costs include waste disposal for spent

[14] The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* (USEPA, 2018c) contains more complete discussion of the WBS models and the cost estimating approach.

resin, but do not include post-treatment costs for corrosion control because blending rates at most entry points should not result in much chloride addition or changes in corrosivity.

For purposes of estimating the costs and benefits, the EPA assumed that CWSs and NTNCWSs in California and Massachusetts would not incur additional cost or realize benefits because these States currently regulate perchlorate at a more stringent level than the proposed MCL and alternative MCL. For each entry point in the UCMR 1 dataset outside of these two States, the EPA compared the maximum observed perchlorate concentration to the MCL to identify those that have an exceedance of the proposed MCL. The EPA assumed that these entry points would incur costs for an additional confirmation sample and would need to implement treatment to meet the MCL. For each entry point, the EPA estimated the design flow and the average flow by service populations based on the Agency's prior analysis of the relationships between these values (USEPA, 2000b). The Agency assumed blending of treated water and untreated water would be used to meet an average treatment target equal to 80 percent of the MCL (for an MCL of 56 μg/L the blending target would be 45 μg/L) given a 95 percent removal effectiveness until perchlorate breakthrough. The Agency applied the capital cost and O&M cost curves from the WBS models to the design and average flows adjusted for blending. When small systems in the UCMR 1 sample incurred treatment costs, the EPA extrapolated the costs on a per capita basis to the estimate of national population exposure derived using the small system population sampling weights.

For the primacy agencies that will implement and enforce the rule (including 49 States, one tribal nation and 5 territories), the EPA estimated upfront costs incurred during the three

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years between rule promulgation and the effective date to read and understand the rule, adopt regulatory changes, and provide training to CWSs and NTNCWSs and Agency staff. Primacy agencies will also have recurring costs to review waiver applications and monitoring reports. Table XII-3 summarizes the labor hour assumptions for these activities. The EPA requests comments on these assumptions.

Table XII-3: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[1]	one time per Agency	416
Provide initial training and assistance to water systems[2]	total per Agency	2,080
Provide initial training to staff[2]	total per Agency	250
Review waiver applications	once every 9 years per eligible system	8
Review monitoring reports	per monitoring event	1

Source (USEPA, 2000a)

1. The EPA assumed that two States that already regulate perchlorate in drinking water would not incur the incremental burdens in this table to regulate perchlorate under the proposed rule because they already incur baseline costs for perchlorate regulation including monitoring costs. The Agency assumed, however, that the two States would incur an average of 40 hours to confirm that their existing requirements are at least as protective as the proposed rule.

2. The EPA assumed that all training hours occur in a single year, although the hours may actually occur over time. The total hour estimates are average values across States.

State labor rates are based on the mean hourly wage rate from Bureau of Labor Statistics (BLS) Standard Occupational Classification code 19-2041 (State Government –Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report (Bureau of Labor Statistics (BLS), 2016 Table 3), for a fully loaded hourly wage rate for States of $50.67. The EPA requests comments on these labor rate assumptions.

The proposed rule provides three years between the effective dates and compliance dates for systems. For the purpose of estimating costs, the EPA assumed that large CWSs would phase

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in administrative costs, including initial monitoring, and upfront administrative costs uniformly over the 3 years following the effective date (i.e., years 4 to 6 of the analysis period). Similarly, the EPA assumed that small CWSs and NTNCSs will phase in these costs over the subsequent three-year period (i.e., years 7 to 9 of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL. Thereafter, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for 9 years (ground water systems), then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring - once every nine years - under subsequent waivers. Systems that are below the MCL without waivers will monitor once per year (surface water systems) or once every three years (groundwater). Consistent with USEPA (2008b), the EPA assumed that 90% of groundwater and 40% of surface water systems that have all entry points below the MCL would obtain waivers.

The EPA estimated the costs over a 35-year analysis period, which includes a 3-year period prior to the effective date to allow for State rule adoption activities, a 3-year period after the effective date to allow initial monitoring among large CWSs, and a 3-year period after that to allow initial monitoring for small CWSs and NTNCWSs. Evaluating costs over 35 years covers a full life cycle of the capital investments that large systems make in the 6th year; the WBS estimates of composite useful life of the equipment and infrastructure investment is approximately 30 years. The EPA assumed that treatment modifications will be completed in the

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final year of the initial monitoring period (i.e., year 6 of the analysis for large CWSs and year 9 for small CWSs and NTNCWSs). The EPA calculated the present value of total costs in each year of the analysis period and discounted to year 1 using both a 3% and 7% discount rate and annualized total present value of costs at the same rates over 35 years to obtain a constant total annual cost estimate to compare to total annual benefits.

Water systems typically recover costs through increased household rates, resulting in increased costs at the household level[15]. To calculate the magnitude of the cost increase for systems that exceed the proposed MCL or alternative MCL, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected CWSs and NTNCWSs and the average household size (U.S. Census Bureau, 2017b). The EPA divided the total annual system-level costs by the number of households served by the system.

C. Method for Estimating Benefits

The EPA has taken an approach in evaluating the benefits for perchlorate that is consistent with the SAB's recommendations for the methodology to inform the MCLG for perchlorate. This approach involves a) using a BBDR model to estimate the impact of perchlorate on maternal thyroid hormone levels during the first trimester of pregnancy, and b) using a dose-response function from the epidemiological literature to model the relationship between altered maternal thyroid hormone levels and offspring IQ. Currently available science

[15] For systems with monitoring costs only, household-level costs will be negligible.

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has limited this quantitative benefits assessment to the relationship between perchlorate and IQ. Given that alterations in thyroid hormones have been associated with other adverse outcomes, including reproductive outcomes (Alexander et al., 2017; Hou et al., 2016; Maraka et al., 2016) and effects on cardiovascular systems (Asvold et al., 2012; Sun et al., 2017) there are likely non-quantified benefits of risk reductions for other endpoints or reduced exposure to co-occurring contaminants, which are addressed below. Uncertainties regarding the quantifiable benefits are also addressed below.

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a CWS or NTNCWS with perchlorate concentrations above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each affected CWS and NTNCWS by the proportion of women of childbearing age (aged 15-44) in the US, which is 19.7 percent (U.S. Census Bureau, 2017a). The number of women of child-bearing age for each entry point was then multiplied by the annual number of live births in the US, or 62 births per 1,000 women (6.2 percent) (Martin, Hamilton, & Osterman, 2017).

The EPA used a two-step dose-response model to estimate health benefits of a reduction in perchlorate exposure as a result of regulating perchlorate in drinking water not to exceed the proposed MCL of 56 μg/L and alternative MCLs of 18 μg/L and 90 μg/L. The first step relates

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changes in perchlorate to changes in maternal free-thyroxine (fT4) during the first trimester of pregnancy using the EPA's BBDR model. Because the dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, this first-step analysis is repeated for several categories of iodine intake. For the BBDR simulations, the EPA used the 90th percentile ingestion rate to be consistent with the MCLG modeling approach, which may overstate the exposure in the simulation.

The second step of the dose-response model subsequently relates the predicted changes in maternal fT4 from the BBDR model to changes in child IQ using the function estimated in the EPA independent analysis of the Korevaar et al., (2016) study data. Ultimately, the changes in IQ are estimated for each impacted iodine intake group, and all of the impacted iodine intake groups' IQ decrements are averaged together based on the proportion of individuals in each iodine intake category. Table XII-4 shows the specific iodine intake groups and the proportion of non-pregnant women of childbearing age that fall into each group.

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Table XII-4: Proportion of Population based on Maternal Iodine Intake Status

Iodine Intake Range (µg/ day) used for Benefits Analysis	Proportion of the population
0 to <55	7.14%
55 to <60	2.15%
60 to <65	1.06%
65 to < 70	1.86%
70 to <75	1.31%
75 to <80	3.10%
80 to <85	2.62%
85 to <90	1.20%
90 to <95	1.83%
95 to <100	2.94%
100 to <125	13.56%
125 to <150	9.08%
150 to <170	10.31%
170 to <300	24.47%
≥300	17.36%

Source: U.S. EPA (2019a).

These changes in child IQ are then monetized using the EPA's estimate of the value of an IQ point. This estimate reflects the discounted present value of lifetime income reductions attributable to a 1-point reduction in IQ at birth. Therefore, the present value depends on the discount rate. At a 3 percent discount rate, the estimate is $18,686 per IQ point; at a 7 percent discount rate the estimate is $3,631.

Other potential benefits not quantified or monetized include additional avoided health effects which cannot currently be monetized, improved public perception of water quality, as well as a possible reduction of other co-occurring contaminants that target the thyroid, such as nitrate, as a result of water treatment for removal of perchlorate. For example, all of the treatment technologies evaluated for this rule (ion exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate from drinking water. Section XIII provides additional discussion of uncertainties in this analysis.

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D. *Comparison of Costs and Benefits*

This section provides the estimates of costs and benefits that the EPA derived using the methods described above. It includes estimates for the proposed and alternative MCLs.

For the proposed MCL of 56 µg/L, Table XII-5 summarizes the total estimated cost of the proposed rule to water systems and primacy agencies, and Table XII-6 summarizes the estimated per-household cost for the system incurring treatment costs[16]. Table XII-7 summarizes the estimated benefits. In both instances, the estimates based on the UCMR 1 sample are also national estimates because treatment costs occur only at large systems; there are no small system treatment costs or related benefits to extrapolate.

Table XII-5: Summary of Total Annualized Costs at MCL of 56 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.65	$0.70
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.38
Drinking Water Systems Costs Subtotal	$6.58	$7.07
State Administration Costs	$3.09	$3.20
Total Costs	$9.67	$10.28

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-6: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 56 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$11	$14

[16] For all households served by all of the systems subject to the monitoring costs as well as MCL compliance, the average annual cost is less than $0.20.

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Cost Range	3% Discount	7% Discount
Average	$40	$47
Maximum	$69	$80

Source: (USEPA, 2019a).

Table XII-7: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 56 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	243	$3.57	$0.60
Central	136	$2.00	$0.34
Lower	30	$0.44	$0.07

Source: (USEPA, 2019a)

For the alternative MCL of 18 µg/L, Table XII-8 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-9 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-10 summarizes the quantified benefits. At this threshold, one entry point for one small system in the UCMR 1 data had an exceedance. Therefore, the EPA extrapolated the treatment costs and benefits from the UCMR 1 estimates to national estimates based on sampling weights.

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Table XII-8: Summary of Total Annualized Costs at MCL of 18 µg/L (Millions; 2017$)

Cost Component	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Drinking Water Systems Treatment Costs	$6.92	$7.29	$7.92	$8.37
Drinking Water Systems Monitoring and Administration Costs	$5.94	$6.38	$5.94	$6.38
Drinking Water Systems Costs Subtotal	$12.85	$13.67	$13.86	$14.75
State Administration Costs	$3.09	$3.21	$3.09	$3.21
Total Costs	$15.95	$16.88	$16.95	$17.96

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA calculated per-capita costs for the system and extrapolated to national level based on this population estimate.

2. Costs include monitoring for all CWS and NTNCWS. Under 40 CFR 141.29 some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided primacy agencies, with EPA concurrence, allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and primacy agency decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-9: Summary of Household-Level Annual Costs for Systems Treating to Comply with the MCL at 18 µg/L (2017$)

Cost Range	3% Discount (UCMR 1)[1]	7% Discount (UCMR 1)[1]	3% Discount (National)[1]	7% Discount (National)[1]
Minimum	$18	$24	$18	$24
Average	$38	$46	$38	$46
Max	$72	$84	$72	$84

Source: (USEPA, 2019a)

1. National cost estimates include extrapolation for one small system entry point to national estimates based on sampling weights. The per-household costs are the same for the sample and national extrapolations because the small system cost extrapolation occurs on a per-capita basis.

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Table XII-10: Total and Annualized Benefits of Avoided Lost IQ Decrements at 18 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ		UCMR 1		National[1]	
	UCMR 1	National[1]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.50	$1.10	$6.56	$1.11
Central	248	251	$3.65	$0.62	$3.68	$0.62
Lower	54	55	$0.80	$0.13	$0.80	$0.14

Source: (USEPA, 2019a)

1. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is one of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

For the alternative MCL of 90 µg/L, Table XII-11 summarizes the total cost of the proposed rule to water systems and primacy agencies, and Table XII-12 summarizes the per-household cost for systems requiring treatment, which vary across the systems. Table XII-13 summarizes the quantified benefits. At this threshold, no small systems in the UCMR 1 data had an exceedance. Therefore, treatment costs and benefits for the UCMR 1 data are the national estimates.

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Table XII-11: Summary of Total Annualized Costs at MCL of 90 µg/L (Millions; 2017$)

Cost Component	3% Discount	7% Discount
Drinking Water Systems Treatment Costs	$0.49	$0.52
Drinking Water Systems Monitoring and Administration Costs[1]	$5.93	$6.37
Drinking Water Systems Costs Subtotal	$6.42	$6.89
State Administration Costs	$3.09	$3.20
Total Costs	$9.51	$10.10

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. Costs include monitoring for all CWS and NTNCWS. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate provided States allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on system and State decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.

Table XII-12: Summary of Household-Level Annual Costs for Systems Treating to Comply with MCL at 90 µg/L (2017$)

Cost Range	3% Discount	7% Discount
Minimum	$65	$76
Average	$65	$76
Maximum	$65	$76

Source: (USEPA, 2019a). There is no variation in costs because treatment costs occur at one entry point. The household costs are slight lower compared to the maximum cost at 56 µg/L because treatment costs to meet an MCL of 90 µg/L are lower than the costs to meet an MCL of 56 µg/L.

Table XII-13: Summary of Total Annualized Benefits of Avoided Lost IQ Decrements at MCL of 90 µg/L (Millions; 2017$)

Korevaar β distribution	Annual Delta IQ	3% Discount	7% Discount
Upper	222	$3.26	$0.55
Central	124	$1.83	$0.31
Lower	27	$0.40	$0.07

Source: (USEPA, 2019a)

Table XII-14 provides a comparison of benefits and costs for three MCL values. First, the table shows the total annual costs and total annual benefits for each MCL. In all cases, the total costs are substantially higher than the potential range of quantifiable benefits. The table also

shows the incremental impact on costs and benefits between an MCL of 56 μg/L and an MCL of 18 μg/L and between an MCL of 90 μg/L and 56 μg/L.

Section 1412(b)(4)(C) of the SDWA requires that when proposing a national primary drinking water regulation, "the Administrator shall publish a determination as to whether the benefits of the maximum contaminant level justify, or do not justify, the costs." The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the States. Based on a comparison of costs and benefits estimated at the proposed MCL of 56 μg/L using the best available science and data, the EPA Administrator has determined based upon the available information that the benefits of establishing an NPDWR for perchlorate do not justify the associated costs.

Under these circumstances, Section 1412(b)(6)(A) of the SDWA provides, with exceptions not relevant here, that "the Administrator *may*, after notice and opportunity for public comment promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits." The EPA has evaluated the benefits and costs of alternative MCL values of 18 μg/L and 90 μg/L. However, based upon the available information the Administrator also finds that the benefits of an NPDWR at the alternative MCL values would not justify the resulting rule costs. The alternative MCLs would not increase net benefits, while compliance costs associated mainly with nationwide CWS monitoring requirements would remain relatively similar. Consistent with the discretion afforded the Agency by SDWA Section 1412(b)(6)(A) to decide whether or not to adjust an MCL to a level where the benefits justify the costs, the EPA is however proposing, and may finalize, the

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MCL of 56 µg/L notwithstanding the Agency's determination that benefits would not justify the costs.

Table XII-14: Comparison of Annual Costs and Benefits by MCL (Millions; 2017$)

MCL Value	Cost 3% Discount	Benefit 3% Discount	Cost 7% Discount	Benefit 7% Discount
UCMR 1				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$15.95	$0.80 - $6.50	$16.88	$0.13 - $1.10
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$6.28	$0.36 - $2.93	$6.60	$0.06 - $0.50
National				
90 µg/L	$9.51	$0.40 - $3.26	$10.10	$0.07 - $0.55
56 µg/L[1]	$9.67	$0.44 - $3.57	$10.28	$0.07 - $0.60
18 µg/L	$16.95	$0.80 - $6.56	$17.96	$0.14 - $1.11
Incremental (from 90 µg/L to 56 µg/L)	$0.16	$0.04 - $0.31	$0.18	$0.0 – 0.05
Incremental (from 56 µg/L to 18 µg/L)	$7.28	$0.36 - $2.99	$7.69	$0.07 - $0.51

Source: (USEPA, 2019a). Detail may not sum to total because of independent rounding.
1. For the proposed MCL of 56 µg/L and the alternative MCL of 90 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for one small system entry point to national estimates based on sampling weights described above.

XIII. Uncertainty Analysis

The EPA has presented an extensive discussion of the uncertainties in the key analyses informing this proposal in the uncertainty section of the MCLG Approaches Report and the uncertainties section of the Economic Analysis document (*USEPA, 2018b; USEPA, 2019a)*. A summarized description of these uncertainties are presented below.

A. Uncertainty in the MCLG Derivation

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Each input into the analysis to inform the MCLG is a decision point associated with uncertainty. There is uncertainty in different aspects of the BBDR model, ranging from structural and functional relationships to specific parameter values for early pregnancy. There are very few data available to calibrate the pharmacokinetic aspects of the model, particularly at the life stage of interest. Also, the BBDR model does not explicitly consider the effect of the presence of other goitrogens (e.g. thiocyanate, nitrate) or effects of thyroid disease states. Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. Additional uncertainty is introduced by linking the BBDR model estimates of maternal fT4 to altered neurodevelopment in offspring. None of the studies used to evaluate potential adverse neurodevelopmental outcomes in offspring born to hypothyroxinemic mothers was performed in the U.S. None of the studies measured perchlorate exposure. Not all the studies measured iodide levels in the study populations. The state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. There are numerous indices used to assess neurodevelopmental impacts and there is some uncertainty regarding the selection of IQ as the critical endpoint for setting the MCLG.

A recently published paper evaluating the EPA's BBDR model and MCLG Approaches, reiterated the uncertainties the Agency identified in its analyses and questions the use of these quantitative tools for perchlorate in a regulatory context (Clewell et al., 2019).

B. Uncertainty in the Economic Analysis

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The EPA provides discussions regarding several sources of uncertainty in the benefit and cost estimates in the Health Risk Reduction and Cost Analysis (USEPA, 2019a). Table XIII-1 provides a summary of sources of uncertainty and their potential effects on estimated costs and benefits. The following discussion addresses uncertainties specific to the benefits analysis.

Table XIII-1. Sources of Uncertainty in Economic Analysis

Description	Potential effect[1]
Baseline Occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water).	± (benefits and costs will change in the same direction)
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 µg/L or 90 µg/L and that one small system would exceed 18 µg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than the MCLs that are not captured in the national extrapolation results.	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates.	± (benefits and costs will change in the same direction)
Benefits Analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum.	± (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4.	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.	± (benefits only)
The EPA used a 90th percentile water intake rate to derive the MCLG and the dose-response equations for the benefits analysis. This approach results in a protective MCLG value, but may overstate intake for the benefits analysis[2].	+ (benefits only)

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Description	Potential effect[1]
The IQ valuation uses estimates that the EPA derived using the same approach as Salkever (1995). Results from other IQ valuation studies might result in higher or lower benefit estimates.	± (benefits only)
The benefits analysis is based on a single health endpoint and the value of the endpoint is based solely on lost earnings.	– (benefits only)
Cost Analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits.	+ (benefits and costs will change in the same direction)
The EPA assumed that all entry points requiring treatment would implement ion exchange, which may overestimate costs if non-treatment is an option for one or more entry points or underestimate costs if site-specific conditions result in higher costs at one or more entry points.	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary.	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle.	– (costs only)
The EPA assumed that 90% of ground water systems and 40% of surface water systems obtain perchlorate monitoring waivers; the actual percentages may vary.	± (costs only)

1. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty, i.e., benefits and/or costs could be underestimated or overestimated.
2. The EPA did not include a perchlorate dietary dose in the benefits analysis, which would be unchanged between baseline and proposed MCL scenarios if many areas do not irrigate with drinking water. For people who obtain a significant portion of their fruit, vegetables, and milk from areas irrigated with the water from the same sources as the drinking water, we would expect their exposure may drop with the reduction of perchlorate in food products used locally. Because of this and the natural log form of the IQ response function, this approach may slightly understate the avoided IQ decrement estimates.

The EPA acknowledges the uncertainty regarding the quantitative health risk reduction. In particular, the Agency assumed it could estimate risk reductions based on evidence of a quantifiable relationship between thyroid hormone changes and neurodevelopmental outcomes.

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There are a number of potential benefits of reducing perchlorate in drinking water that were not quantified as part of this analysis, which may result in an underestimate of actual benefits. As described by the SAB "children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood (Man et al., 1991; Pop et al., 1999; Pop et al., 2003; Kooistra et al., 2006)" (p. 10, SAB for the U.S. EPA, 2013). The EPA's literature review identified potential relationships between maternal thyroid hormone alterations and the risk of schizophrenia, ADHD, expressive language delay, reduced school performance and increased odds of autism, among others, none of which are being currently quantified in this assessment. Other potentially omitted benefits include risks associated with effects of thyroid disorders in adults, including cardiovascular disease risk; changes in thyroid hormone levels and their relationship with total cholesterol, LDL cholesterol, and triglycerides; as well as a possible relationship between increases in TSH and risk of fatal coronary heart disease. Treating for perchlorate in drinking water could also potentially remove nitrate, which is a co-occurring contaminant and a goitrogen. These additional potential health endpoints are not monetized in this benefits analysis. The assumptions used to account for the previously mentioned variability of the BBDR model inputs and uncertainty surrounding the relationship between maternal fT4 and child IQ discussed above may result in an overestimate of the monetized benefits. Because IQ is a surrogate for broad range of potential neurodevelopmental risks, it is unclear whether the analysis as a whole over- or under-estimates the monetized benefits of a reduction of perchlorate in drinking water.

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XIV. Request for Comment on Proposed Rule

While all comments relevant to the national primary drinking water regulation for perchlorate proposed today will be considered by the EPA, comments on the following issues will be especially helpful to the EPA in developing a final rule. The EPA specifically requests comment on the following topics.

- The adequacy and uncertainties of the BBDR model developed by the EPA to predict thyroid hormone level changes caused by perchlorate exposure to pregnant women with low iodide intake, including the model and model parameters and assumptions (Section III and Approaches Report).
- The adequacy and uncertainties of the EPA's review and application of the epidemiologic literature to quantify the relationship between thyroid hormone changes in pregnant women and neurodevelopmental effects including the assumptions, the selection of the approach used, and the study used (Section III and Approaches Report).
- The adequacy and uncertainties of the methodology to derive the MCLG including points of departure, assumptions, uncertainty factor, and relative source contribution (Section III and Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water).
- The proposed MCLG and MCL of 56 μg/L as well as the alternative MCLG and MCL values of 18 μg/L and of 90 μg/L.
- The feasibility of the proposed MCL of 56 μg/L as well as the feasibility of the alternative MCLs of 18 μg/L and 90 μg/L.

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- The adequacy of the underlying assumptions and analysis of occurrence (Section VI).
- The costs and availability of Treatment Technologies (Section X).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate costs and describe unquantified costs including the estimates of monitoring frequency, likelihood of systems receiving a monitoring waiver, the administrative labor rate and the operator labor rate. (Section XII and the Health Risk Reduction Cost Analysis).
- The adequacy of the underlying estimates, assumptions and analysis used to estimate benefits and describe unquantified benefits (Section XII and the Health Risk Reduction Cost Analysis).
- Potential implementation challenges associated with the proposed perchlorate regulation that the EPA should consider, specifically for small systems.
- The Administrator's finding in accordance with Section 1412(b)(4)(C) of the SDWA that the benefits of the proposed 56 μg/L MCL for perchlorate do not justify the costs, and the information that supports that determination as described in Section XII of this notice.
- The Administrator's proposal to, consistent with the discretion afforded him by SDWA Section 1412(b)(6)(A), adopt an MCL of 56 μg/L notwithstanding the Agency's SDWA Section 1412(b)(4)(C) determination that the benefits of the MCL would not justify its costs.
- The Agency's conclusion that no alternative MCL, including the alternative MCL values of 18 μg/L and 90 μg/L discussed above, would "maximize health risk reduction benefits at a cost that is justified by the benefits" and the information and analytical approaches used to

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arrive at that conclusion. The EPA is especially interested in comments suggesting other approaches to deriving an MCL for which the benefits justify the costs.

XV. Request for Comment on Potential Regulatory Determination Withdrawal

The EPA is soliciting comments on withdrawing the 2011 Regulatory Determination (see Section II-C, Regulatory History) based on several factors. First, the findings, described in the occurrence section (section VI) and in the updated health effects assessment (Section III), suggest that perchlorate does not occur in public water systems with a frequency and at levels of public health concern[17] and suggest that the regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. The proposed regulation would require over sixty thousand public water systems to monitor for perchlorate, but the available data indicates that very few would find it at levels of public health concern. Specifically, perchlorate occurrence information suggests that at an MCL of 56 μg/L only 2 systems (0.004% of all water systems in the U.S.) would exceed the regulatory threshold. Even at an MCL of 18 μg/L, there would only be 15 systems (0.03% of all water systems in the U.S.) that would exceed the regulatory threshold. Only one system would exceed the alternative MCL of 90 μg/L.

The EPA notes that in 2008, the EPA stated in its preliminary regulatory determination that perchlorate did not occur with a frequency and at levels of public health concern in public water systems based upon the health effects and occurrence information available at that time,

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[17] As shown in Section VI of this notice there is infrequent occurrence of perchlorate at either 56 μg/L, 18 μg/L or 90 μg/L, which are the possible levels expected to cause adverse human health effects.

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which indicated that 0.8% of public water system had perchlorate at levels exceeding the HRL of 15 μg/L. The EPA also stated that there was not a meaningful opportunity for a NPDWR to reduce health risks based upon the estimates at that time that 0.9 million people had perchlorate levels above the HRL.

The EPA further notes that the Agency has previously determined CCL1 and CCL2 contaminants did not occur with frequency at levels of public health concern when the percentage of water systems exceeding the HRL were greater than the frequency of perchlorate occurrence level at the proposed MCL (0.004% of all water systems in the U.S.). For example, in 2003 the EPA determined that aldrin did not occur with a frequency and at levels of public health concern based upon data that showed 0.2% of water systems had aldrin at levels greater than the HRL. The EPA also concluded that there was not a meaningful opportunity for health risk reduction for persons served through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 1 million people (USEPA, 2003). In 2008 the EPA determined that DCPA Mono- and Di-Acid degradates did not occur with a frequency and at levels of public health concern based on data that showed 0.03% of water systems exceeded the HRL. The EPA also included that there was not a meaningful opportunity for health risk reduction through a drinking water regulation based on this occurrence data and the estimate that these systems above the HRL served approximately 100,000 people (USEPA, 2008e).

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SDWA Section 1412(b)(1)(A)(iii) states that the determination regarding the meaningful opportunity is "in the sole judgement of the Administrator" and therefore there may be other factors that contribute to this determination for any given contaminant.

If, after consideration of public comment, the EPA withdraws the perchlorate regulatory determination, there will be no NPDWR for perchlorate, although the EPA can re-list perchlorate on the CCL and proceed to regulation in the future if the occurrence or risk information changes. As with other unregulated contaminants, the EPA could address the limited instances of elevated levels of perchlorate by working with the states or using its SDWA Section 1431 imminent and substantial endangerment or Section 1412(b)(1)(f) health assessment authorities, as appropriate. The EPA also requests comments on what guidance it could provide the public if the regulatory determination for perchlorate is withdrawn.

XVI. Statutory and Executive Order Reviews

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

This action is a significant regulatory action since it raises novel legal or policy issues. It was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

The EPA evaluated the potential costs to States and utilities and the potential benefits of the proposed rule. This analysis, *Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a)* is available in the docket and is summarized in section XI.

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B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Cost

This action is expected to be an Executive Order 13771 regulatory action. Details on the estimated costs of this proposed rule can be found in the EPA's analysis of the potential costs and benefits associated with this action.

C. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The monitoring information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule including adopting the NPDWR into state regulations, providing training to state and PWS employees, updating their monitoring data systems, and reviewing system monitoring data and waiver requests. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) would not begin until after Year 3 due to the proposed effective date of this rule.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,159. The frequency of response (average responses per respondent) is 1 for primacy agencies,

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annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three-year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for the EPA's regulations are listed in 40 CFR part 9.

Submit your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to the EPA at the public docket established for this rule, which includes the ICR, Docket ID No. **EPA-HQ-OW-2018-0780**. You may also send your ICR-related comments to OMB's Office of Information and Regulatory Affairs via email to OIRA_submission@omb.eop.gov, Attention: Desk Officer for the EPA. Since OMB is required to make a decision concerning the ICR between 30 and 60 days after receipt, OMB

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must receive comments no later than **[insert date 30 days after publication in the *Federal Register*]**. The EPA will respond to any ICR-related comments in the final rule.

D. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. The Agency has determined that the proposed MCL of 56 μg/L will not result in annual costs that exceed one percent of revenue for small systems affected by the proposed rule.

The small entities subject to the requirements of this action are public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the Federal Register, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that would affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. In order to meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 μg/L, the UCMR 1 monitoring data indicate that no small systems would be required to incur costs to reduce the levels of perchlorate in drinking water, therefore, all small PWSs will incur

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monitoring costs only. Impacts on small entities are described in more detail in Chapter 7 of the Health Risk Reduction Cost Analysis of the Proposed Perchlorate Rule (USEPA, 2019a). Table XII-1 and Table XII-2 show the annual compliance costs of the proposed rule on the small entities by system size for public and private systems, respectively. Based on a comparison of annual costs with annual revenue estimates, the EPA has determined that no small systems will experience an impact of one percent or greater of average annual revenues (USEPA 2019a).

Table XII-1: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Public CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$224,248	$88 (0.04%)	$94 (0.04%)
Population served 101-500	$197,315	$88 (0.04%)	$94 (0.05%)
Population served 501-3,300	$202,382	$88 (0.04%)	$94 (0.05%)
Population served 3,301-10,000	$1,092,187	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS (USEPA, 2009c Table 65) and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers (BLS, 2018a). Revenues include all sources of revenue including water revenue, non-water revenue, and municipal transfers to water systems.

b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

Table XII-2: Annualized Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small Private CWSs by Size Category

Size Category	Average Annual Revenues[a]	3% Discount[b]	7% Discount[b]
Population served <100	$139,911	$88 (0.06%)	$94 (0.07%)
Population served 101-500	$351,974	$88 (0.03%)	$94 (0.03%)
Population served 501-3,300	$254,706	$88 (0.03%)	$94 (0.03%)
Population served 3,301-10,000	$951,692	$88 (0.01%)	$94 (0.01%)

Source: Perchlorate Benefit-Cost Analysis Spreadsheet available in the proposed rule docket (EPA-HQ-OW-2018-0780)

a. Based on the CWSS (USEPA, 2009c Table 65) and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers (BLS, 2018a). Revenues include all sources of revenue including water revenue and non-water revenue.

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b. Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually (Exhibit 5 5), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

E. Unfunded Mandates Reform Act

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538. The action imposes minimal enforceable duty on any state, local or tribal governments or the private sector

Based on the cost estimates detailed in Section XI, the EPA determined that compliance costs in any given year would be below the threshold set in UMRA, with maximum single-year costs of approximately $10.2 million. The EPA has determined that this rule contains a federal mandate that would not result in expenditures of $100 million or more for State, local, and Tribal governments, in the aggregate, or the private sector in any one year.

F. Executive Order 13132: Federalism

This action does not have federalism implications. It will not have substantial direct effects of greater than $25 million on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Annual costs are estimated to range from $9.6 million at a 3 percent discount rate to $10.2 million using a 7 percent, with $6.5 million to $7.0 million annually accruing to public entities. The EPA has concluded that this proposed rule may be of interest because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs.

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G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government would not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They would bear an estimated total annualized cost of $74,100 at a 3 percent discount rate ($79,625 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes which included a webinar with interested tribes on February 28, 2012, to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA 2012a). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule would be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA policy to promote communications between the EPA and

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Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

H. Executive Order 13045: Protection of Children from Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 because it is not economically significant as defined in Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the Health Effects Technical Support Document (USEPA 2018a) and described in section III of this preamble. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive subpopulation – offspring of pregnant women exposed to perchlorate during the first trimester – and established a proposed MCLG that is protective of this subpopulation as well as other children. The EPA also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in the Health Risk Reduction and Cost Analysis for the proposed rule (USEPA 2019a) and is summarized in section XI of this preamble. Copies of the Health Effects Technical Support Document and Economic Analysis and supporting information are available in the public docket for today's proposal.

I. Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a ''significant energy action'' as defined in Executive Order 13211, ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355 (May 22, 2001)) because it is not likely to have a significant adverse effect

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on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical

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power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

J. National Technology Transfer and Advancement Act of 1995

The proposed rule could involve voluntary consensus standards in that it would require monitoring for Perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. The EPA methods 314.0, 314.1, 314.2, 331.0, and 332.0 incorporate quality control criteria which allow accurate quantitation of perchlorate. Additional information about the analytical methods is available in section VII of this notice.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring. The EPA welcomes comments on this aspect of the proposed rulemaking and, specifically, invites the public to identify potentially-applicable voluntary consensus standards and to explain why such standards should be used in this regulation.

K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

The EPA has determined that this proposed rule would not have disproportionately high and adverse human health or environmental effects on minority or low-income populations because it would increase the level of environmental protection for all affected populations

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without having any disproportionately high and adverse human health or environmental effects on any population, including any minority or low-income population.

The public is invited to comment on this aspect of the proposed rulemaking and, specifically, to recommend additional methods to address Environmental Justice concerns from establishing a drinking water rule for perchlorate in drinking water.

XVII. Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412(d) and 1412(e) of the Safe Drinking Water Act (SDWA), the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services; and with the EPA Science Advisory Board. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the National Drinking Water Advisory Council, Fall 2012 Meeting Summary Report (NDWAC, 2012b) and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during the development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA Science Advisory Board (SAB) on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive a Maximum Contaminant Level Goal (MCLG) for perchlorate (USEPA, 2012; NRC, 2005). On May 29, 2013, the EPA received significant input

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from SAB, summarized in the report, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate (USEPA, 2013a).

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking process for perchlorate (USEPA 2013b). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/pharmacodynamic (PD), or biologically based dose-response (BBDR), models that incorporate all available health related information on perchlorate to predict changes in thyroid hormones in sensitive life stages exposed to different dietary iodide and perchlorate levels (USEPA 2017). As recommended by SAB, the EPA developed these models based upon perchlorate's mode of action (i.e., iodide uptake inhibition by the thyroid) (USEPA 2013a). Additional details are in section III.C. of this notice and in the Health Effects of Perchlorate support document located in the docket for this proposed rule.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine intake and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA 2013a).

On March 25, 2019, the EPA consulted with the Department of Health and Human Services (HHS). The EPA provided information to HHS officials on the draft proposed

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perchlorate regulation and considered HHS input as part of the interagency review described in section XVII.A.

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List of Subjects in 40 CFR Parts 141, and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated: MAY 2 3 2019

Andrew R. Wheeler,

Administrator.

For the reasons stated in the preamble, the Environmental Protection Agency proposes to amend 40 CFR part 141 and 40 CFR part 142 as follows:

PART 141 - NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

   Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. Amend § 141.6 by revising paragraph (a) and adding paragraph (l).

3. Amend § 141.23 by:

   a. Revising the title in the table in paragraph (a)(4)(i);

   b. Adding "Perchlorate" in alphabetical order, in the table in paragraph (a)(4)(i);

   c. Adding "perchlorate" in paragraph (a)(5);

   d. Adding "perchlorate" in alphabetical order, in paragraph (c);

   e. Adding paragraph (c)(10);

   f. Adding "perchlorate" in alphabetical order, in paragraph (f)(1);

   g. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(1);

   h. Adding "perchlorate" in alphabetical order, to the first sentence in paragraph (i)(2);

   i. Revising paragraph (i)(3);

   j. Revising paragraph (k)(1);

   k. Adding "perchlorate" in alphabetical order, to the second sentence in paragraph (k)(1);

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l. Adding an entry for "21. Perchlorate" in alphabetical order, in the table in paragraph (k)(1);

m. Adding "perchlorate" in alphabetical order, to paragraph (k)(2);

n. Adding "Perchlorate" in alphabetical order, in the table in paragraph (k)(2);

o. Adding "perchlorate" in alphabetical order, to the third sentence in paragraph (k)(3); and

p. Adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (k)(3)(ii).

4. Amend § 141.51 by adding an entry for "Perchlorate" in alphabetical order, in the table in paragraph (b).

5. Amend § 141.60 by adding paragraph (b)(5).

6. Amend § 141.62 by:

a. Adding an entry (17) for "Perchlorate" in paragraph (b);

b. Adding an entry for "Perchlorate" in alphabetical order, to the table in paragraph (c);

c. Adding an entry "14 = Biological Treatment" in the table Key to BATs in paragraph (c);

d. Adding paragraph (e); and

e. Adding a table in paragraph (e).

7. Amend Appendix A to Subpart O of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART O OF PART 141 – REGULATED CONTAMINANTS."

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8. Amend Appendix A to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX A TO SUBPART Q OF PART 141 - NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTIFICATION."
9. Amend Appendix B to Subpart Q of Part 141 by adding an entry for "Perchlorate" in the table entitled "APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION."

The revisions and additions read as follows:

Subpart A—General

*****

§ 141.6 Effective Dates.

(a) Except as provided in paragraphs (b) through (l) of this section the regulations set forth in this part shall take effect on June 24, 1977.

*****

(l) The regulations contained in the revisions to §§141.23(a)(4)(i), 141.23(a)(5), 141.23(c),141.23(f)(1), 141.23(i)(1)-(2), 141.23(k)(1)-(3), 141.23(k)(3)(ii), 141.51(b), 141.60(b)(5), 141.62(b), 141.62(c), 141.62(e), Appendix A to Subpart O and Appendix A and B to Subpart Q are effective for the purposes of compliance on [insert date].

Subpart C—Monitoring and Analytical Requirements

*****

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§141.23 Inorganic chemical sampling and analytical requirements.

*****

(a)***

(4)***

(i)***

DETECTION LIMITS FOR INORGANIC CONTAMINANTS (COMPOSITED SAMPLES)

Contaminant	MCL (mg/l)	Methodology	Detection limit (mg/l)
*******	*******	*******	*******
Perchlorate	0.056	Ion Chromatography	0.00053
		Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection	0.00003
		Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection	0.000012-0.000018
		Liquid Chromatography Electrospray Ionization Mass Spectrometry	0.000005 (Tandem Mass Spectrometry [MS/MS]) 0.000008 (Selected Ion Monitoring [SIM])
		Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	0.00002
*******	*******	*******	*******

*****

*****

(c)***

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(10) Community water systems and non-transient non-community water systems must conduct initial monitoring for perchlorate as follows:

(i) Community water systems serving greater than 10,000 persons without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2023, and December 31, 2025.

(ii) Community water systems serving 10,000 or fewer persons and non-transient non-community water systems without acceptable historic data, as defined below, must collect four consecutive quarterly samples at all sampling points between January 1, 2026, and December 31, 2028.

(iii) Grandfathering of data: States may allow historical monitoring data collected at a sampling point to satisfy the initial monitoring requirements for that sampling point, for the following situations.

(A) To satisfy initial monitoring requirements, community water systems serving greater than 10,000 persons having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022. Community water systems serving 10,000 or fewer persons and non-transient non-community water systems having only one entry point to the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2023, and December 31, 2025.

(B) To satisfy initial monitoring requirements, a system with multiple entry points and having appropriate historical monitoring data for each entry point to the distribution

system may use the monitoring data from the compliance monitoring period that began between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems.

(C) To satisfy initial monitoring requirements, a system with appropriate historical data for a representative point in the distribution system may use the monitoring data from the compliance monitoring period between January 1, 2020, and December 31, 2022, for community water systems serving greater than 10,000 persons and between January 1, 2023, and December 31, 2025, for community water systems serving 10,000 or fewer persons and for non-transient non-community water systems, provided that the State finds that the historical data satisfactorily demonstrate that each entry point to the distribution system is expected to be in compliance based upon the historical data and reasonable assumptions about the variability of contaminant levels between entry points. The State must make a written finding indicating how the data conforms to these requirements.

(iv) The State may waive the final two quarters of initial monitoring for perchlorate for a sampling point if the results of the samples from the previous two quarters are below the detection limit.

*****

(i)***

(3) Compliance with the maximum contaminant level for nitrate, nitrite and perchlorate is determined based on one sample if the levels of these contaminants are below the MCLs. If the level of perchlorate exceeds the MCL in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(1) and compliance shall be based on the average of the initial and confirmation sample. If the levels of nitrate and/or nitrite exceed the MCLs in the initial sample, a confirmation sample is required in accordance with paragraph 141.23(f)(2) and compliance shall be based on the average of the initial and confirmation sample.

*****

(k)***

(1) Analysis for the following contaminants shall be conducted in accordance with the methods in the following table, or the alternative methods listed in Appendix A to subpart C of this part, or their equivalent as determined by the EPA.

*****

Contaminant	Methodology[13]	EPA	ASTM[3]	SM[4] (18th, 19th ed.)	SM[4] (20th ed.)	SM Online[22]	Other
******	******	*******	*******	*******	*******	*******	*******
Perchlorate	Ion Chromatography	314.0					
	Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed	314.1					

	Conductivity Detection Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection Liquid Chromatography Electrospray Ionization Mass Spectrometry Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	 314.2 331.0 332.0					
******	*******	*******	*******	*******	*******	*******	*******

*****

[3]Annual Book of ASTM Standards, ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428, http://www.astm.org.; Annual Book of ASTM Standards 1994, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1996, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 1999, Vols. 11.01 and 11.02; Annual Book of ASTM Standards 2003, Vols. 11.01 and 11.02.

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[4]Standard Methods for the Examination of Water and Wastewater, American Public Health Association, 800 I Street NW., Washington, DC 20001-3710; Standard Methods

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for the Examination of Water and Wastewater, 18th edition (1992); Standard Methods for the Examination of Water and Wastewater, 19th edition (1995); Standard Methods for the Examination of Water and Wastewater, 20th edition (1998).The following methods from this edition cannot be used: 3111 B, 3111 D, 3113 B, and 3114 B.

*****

[13]Because MDLs reported in EPA Methods 200.7 and 200.9 were determined using a 2x preconcentration step during sample digestion, MDLs determined when samples are analyzed by direct analysis (i.e., no sample digestion) will be higher. For direct analysis of cadmium and arsenic by Method 200.7, and arsenic by Method 3120 B, sample preconcentration using pneumatic nebulization may be required to achieve lower detection limits. Preconcentration may also be required for direct analysis of antimony, lead, and thallium by Method 200.9; antimony and lead by Method 3113 B; and lead by Method D3559-90D, unless multiple in-furnace depositions are made.

*****

[22]Standard Methods Online, American Public Health Association, 800 I Street NW., Washington, DC 20001, available at http://www.standardmethods.org. The year in which each method was approved by the Standard Methods Committee is designated by the last two digits in the method number. The methods listed are the only online versions that may be used.

*****

(2)***

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Contaminant	Preservative[1]	Container[2]	Time[3]
*******	*******	*******	*******
Perchlorate[7]	4 °C	P or G	28 days
*******	*******	*******	******

[1]For cyanide determinations samples must be adjusted with sodium hydroxide to pH 12 at the time off collection. When chilling is indicated the sample must be shipped and stored at 4 °C or less. Acidification of nitrate or metals samples may be with a concentrated acid or a dilute (50% by volume) solution of the applicable concentrated acid. Acidification of samples for metals analysis is encouraged and allowed at the laboratory rather than at the time of sampling provided the shipping time and other instructions in Section 8.3 of EPA Methods 200.7 or 200.8 or 200.9 are followed.

[2]P = plastic, hard or soft; G = glass, hard or soft.

[3]In all cases samples should be analyzed as soon after collection as possible. Follow additional (if any) information on preservation, containers or holding times that is specified in method.

*****

[7] Sample collection for perchlorate shall be conducted following the requirements specified in the approved methods in 141.23(k)(1) or the alternative methods listed in appendix A of subpart C of this part, or their equivalent as determined by the EPA.

*****

(3)***

(ii)***

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Contaminant	Acceptance limit
*******	*******
Perchlorate	± 20% at ≥0.004 mg/L
*******	*******

*****

Subpart F—Maximum Contaminant Level Goals and Maximum Residual Disinfectant Level Goals

*****

§141.51 Maximum contaminant level goals for inorganic contaminants.

*****

(b)***

Contaminant	MCLG (mg/l)
*******	*******
Perchlorate	0.056
*******	*******

*****

Subpart G—National Primary Drinking Water Regulations: Maximum Contaminant Levels and Maximum Residual Disinfectant Levels

§141.60 Effective dates.

(a) ***

(5) The effective date for §141.62(b)(17) is [insert date].

§141.62 Maximum contaminant levels for inorganic contaminants.

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*****

(b)***

Contaminant	MCL (mg/l)
*******	*******
(17) Perchlorate	0.056

(c)***

BAT FOR INORGANIC COMPOUNDS LISTED IN SECTION 141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14
*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

(e)The Administrator, pursuant to section 1412 of the Act, hereby identified in the following table the affordable technology, treatment technique, or other means available to systems serving 10,000

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persons or fewer for achieving compliance with the maximum contaminant level for perchlorate:

SMALL SYSTEM COMPLIANCE TECHNOLOGIES (SSCTs) FOR PERCHLORATE

Small system compliance technology	**Affordability for listed small system categories**
Ion exchange	All size categories.
Reverse osmosis (point of use)	All size categories

Subpart O – Consumer Confidence Reports

*****

APPENDIX A TO SUBPART O OF 141 – REGUATED CONTAMINANTS

Contaminant (units)	**Traditional MCL in mg/L**	**To convert for CCR, multiply by**	**MCL in CCR units**	**MCLG**	**Major sources in drinking water**	**Health effects language**
********	*******	*******	*******	*******	*******	*******
Inorganic contaminants						
********	********	********	*******	*******	*******	*******

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Perchlorate	0.056	1000	56	56	Perchlorate is commonly used in solid rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches and signal flares. Perchlorate may occur naturally, particularly in arid regions such as the southwestern United States and is found as a natural impurity in nitrate salts used to produce nitrate fertilizers, explosives and other products.	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******	*******	*******	*******

Subpart Q – Public Notification of Drinking Water Violations

*****

APPENDIX A TO SUBPART Q OF PART 141 – NPDWR VIOLATIONS AND OTHER SITUATIONS REQUIRING PUBLIC NOTICE[1]

Contaminant	MCL/MRDL/TT violations[2]		Monitoring & testing procedure violations	
	Tier of public notice required	Citation	Tier of public notice required	Citation
*******				
B. Inorganic Chemicals (IOCs)				
*******				

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14. Perchlorate	1	141.62(b)	3	141.23(a), (c), 141.23(f)(1)
*******				

[1] Violations and other situations not listed in this table (e.g., failure to prepare Consumer Confidence Reports), do not require notice, unless otherwise determined by the primacy agency. Primacy agencies may, at their option, also require a more stringent public notice tier (e.g., Tier 1 instead of Tier or Tier 2 instead of Tier 3) for specific violations and situations listed in this Appendix, as authorized under 141.202(a) and 141.203(a).

[2] MCL-Maximum contaminant level, MDRL-Maximum residual disinfectant level, TT-treatment technique

*****

APPENDIX B TO SUBPART Q OF PART 141 – STANDARD HEALTH EFFECTS LANGUAGE FOR PUBLIC NOTIFICATION

Contaminant	MCLG[1] mg/L	MCL[2] mg/L	Standard health effects language for public notification
*******			
C. Inorganic Chemicals (IOCs)			
*******	*******	*******	*******
21. Perchlorate	0.056	0.056	Offspring of pregnant women and infants who drink water containing perchlorate in excess of the MCL could experience delays in their physical or mental development.
*******	*******	*******	*******

[1] MCLG – Maximum contaminant level goal

[2] MCL – Maximum contaminant level

ED_005043_00061621-00161

PART 142 - NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION

1. The authority citation for part 142 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, 300j-9, and 300j-11.

2. In § 142.62:

a. Add an entry for "Perchlorate" to the table in paragraph (b); and

b. Add entry "14 = Biological Treatment" in the table's *Key to BATs* in paragraph (b).

Subpart G – Identification of Best Technology, Treatment Techniques or Other Means Generally Available.

*****

§142.62 Variances and exemptions from the maximum contaminant levels for organic and inorganic chemicals.

*****

(b)***

BAT FOR INORGANIC COMPOUNDS LISTED IN §141.62(b)

Chemical Name	BAT(s)
*******	********
Perchlorate	5, 7, 14

ED_005043_00061621-00162

*******	*******

*****

Key to BATs in Table

*****

5 = Ion Exchange

*****

7 = Reverse Osmosis

*****

14 = Biological Treatment

*****

ED_005043_00061621-00163

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 9/11/2019 11:46:12 AM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: draft summary of perchlorate public comments
Attachments: Perchlorate Comment Summary V2.docx

Revised

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, September 10, 2019 4:04 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Hi Lisa,

Here is a revised version which incorporates previously suggested edits.

- We received 6 comment letters in support of the proposed rule at 56 ppb.
- I cannot categorically confirm that the mass mailing campaign was organized by any group, so I am removing that designation from the summary document.
- From the individual substantive letters
  - 1 supports withdrawal option
  - 1 supports 90 ppb option
  - 6 support 18 ppb option
  - 23 support regulation at a stricter level than 18pbb

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, September 10, 2019 1:44 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: draft summary of perchlorate public comments

Hi Sam,
As follow up can you please:
- Confirm we did not get support for regulation at 56 ppb
- Confirm if NRDC is mentioned as the originator of the mass campaign
- Count the 88 individual comments that 1- support withdrawal, 2- support regulation (at any concentration).

Let me know if you have questions
Thanks,

Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, September 10, 2019 1:30 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Also There are three categories of commenters presented

1. Support withdrawal
2. Support a stricter than proposed standard
3. Neutral

Does this mean there were no commenters in support of the proposed MCLG/MCL?

From: Burneson, Eric
Sent: Tuesday, September 10, 2019 1:27 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Thanks Lisa: My only comment is that unless the comment campaign letters clearly state they are submitting comments organized by NRDC or there is public information from NRDC clearly stating that they organized a comment campaign we should not attribute the campaign to them.
Eric

From: Christ, Lisa
Sent: Tuesday, September 10, 2019 12:27 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: draft summary of perchlorate public comments

Eric,
Attached is a high level summary of the public comments received on the perchlorate proposal. OGC requested a summary to prepare the notice to the court requesting an extension of the consent decree final rule deadline. Let me know if you have questions or would like to discuss.
Lisa

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

NPDWR for Perchlorate Proposal: Summary of Public Comments

EPA received a total of 1,495 comments in response to its perchlorate rulemaking proposal.

- **Mass Mailing Campaign**

1,386 comments were received under a mass mailing campaign. These commenters oppose the proposed Maximum Contaminant Level of 56 µg/L stating that as proposed the MCL is too high to adequately protect the health of communities throughout the country.

- **Individuals**

Eighty-one comment letters with varied levels of complexity were submitted by individuals. These letters cover a wide array of technical and policy issues regarding the perchlorate proposal (88 pages).

  - 6 individuals support the proposed rule a 56 µg/L
  - 1 individual supports the regulatory determination withdrawal alternative
  - 1 individual supports the 90 µg/L alternative
  - 6 individuals support the 18 µg/L alternative
  - 23 individuals support perchlorate regulation at a level stricter than 18pbb

- **Extensive and Substantive Comment Letters**

109 Comment letters containing extensive and substantive technical and policy issues were submitted (657 pages).

The comment letters breakdown as follows:

1. Organizations that support withdrawal:

U.S. Conference of Mayors & the National League of Cities

One letter was jointly submitted by the U.S. Conference of Mayors & the National League of Cities. These organizations urge EPA to withdraw the Regulatory Determination for Perchlorate.

State Agency

- South Dakota

South Dakota Department of Environment and Natural Resources - Recommends that EPA withdraw the Regulatory Determination based on a no meaningful opportunity for risk reduction as required by SDWA

Regulated Stakeholders/Community Water Systems

Two comment letters were submitted by Regulated Stakeholders/Community Water Systems.

- American Water
- El Paso Water

American Water & El Paso Water – Recommend EPA withdraw the Regulatory Determination

Trade/Industry Associations

Seven comment letters were submitted by Trade/Industry Associations

- American Chemistry Council
- American Water Works Association
- Association of Metropolitan Water Agencies
- National Rural Water Association
- Perchlorate Study Group
- The Chlorine Institute
- California Farm Bureau Federation

American Chemistry Council, American Water Works Association, Association of Metropolitan Water Agencies, California Farm Bureau Federation, The Chlorine Institute, Perchlorate Study Group, National Rural Water Association - Recommend that EPA withdraw the Regulatory Determination based on not meeting the statutory requirements of SDWA.

2. Organizations that support stricter (than proposed 56 ppb) regulation of perchlorate:

Regulated Stakeholders/Community Water Systems

Two comment letters were submitted by Regulated Stakeholders/Community Water Systems

- Association of California Water Agencies
- Metropolitan Water District of Southern California

Association of California Water Agencies & Metropolitan Water District of Southern California - Urge EPA to set an MCLG and MCL close to California's standard of 6 µg/L. The federal drinking water standard should be no higher than 18 µg/L.

State Agencies

Six comment letters were submitted by State Agencies

- California
- Massachusetts
- New Jersey
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California - Does not agree with EPA's proposal because it is not health-protective and also believe that the agency has taken approaches that are not fully justified, not appropriate, and that need to be reconsidered.

Massachusetts - Does not support EPA's proposed options for perchlorate in drinking water. MassDEP urges EPA to revise its proposal to fully address perchlorate's toxicity and health protective uncertainty factors.

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Virginia – Recommends EPA to adopt an MCL of 18 µg/L based on possible occurrence above such level due to hypochlorite degradation in the distribution system.

Tribal Stakeholders

Two comment letters were submitted by Tribes

The Salt River Pima-Maricopa Indian Community & the Tohono O'odham Nation – Submitted letters in disagreement with EPA's proposal, and urged the agency to establish an MCL at a level lower than 18 µg/L.

Environmental Advocacy Groups

Five comment letters were submitted by Environmental Advocacy Groups (305 pages)

- Alaska Community Action on Toxics
- Environmental Defense Fund
- Environmental Protection Network
- Environmental Working Group
- Natural Resources Defense Council

These groups strongly disagree with EPA's rulemaking proposal and the suggested regulatory alternatives. All groups suggest that EPA should set a standard for Perchlorate in drinking water no higher than 2 µg/L. In addition, these stakeholders claim that EPA is not following the statutory requirements of SDWA in that the agency failed to consider an adequate margin of safety while establishing a protective public health MCLG.

Public Health Professional Organizations

American Academy of Pediatrics – Disagree with EPA's proposal and urges the agency to set the strongest possible MCLG for Perchlorate.

3. Organizations that are neutral

Association of State Drinking Water Administrators – The board has not taken a position on whether to regulate Perchlorate.

Message

From: Tiago, Joseph [Tiago.Joseph@epa.gov]
Sent: 3/6/2019 6:32:09 PM
To: Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Lousberg, Macara [Lousberg.Macara@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fields, Wanda [Fields.Wanda@epa.gov]
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg
Attachments: Perchlorate Draft Action Memo .SE.3-5-19_v1_OGWDW_030619.docx; Transmittal Memo AA to OPEI. SE.3-5-19_OGWDW_030619.docx; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190305.docx

Hi Sandy,

Thank you for your edits. Your changes have been accepted and two typos corrected as follows:

DR to AW Memo:
Under Impacts: ...and administration requirements consisted of the majority of the annual cost.

DR to BB Memo:
This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs.

Let me know if you have any questions.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 1:08 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

I think you mean the NPRM – the rule is attached.
If not, let me know.
Sandy

From: Tiago, Joseph
Sent: Wednesday, March 06, 2019 1:05 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Thanks, Sandy!

Note the EO 12866 file is blank – not sure it was intentional.

We'll get you a revised version of the memos.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 12:59 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: Use this version - Comments: e-files for the perchlorate pkg
Importance: High

In this version, I also added the San and Rin in the subject line for the Transmittal memo.

Thanks for sending the Perchlorate package. I have a few edits/comments.

1. Thank you for preparing both a transmittal memo and draft action memo. Attached are comments and suggestions.

2. A minor edit regarding the NPRM file name and OMB's requirements. OMB is particular regarding the naming convention. I added the title to the first page of the FRN and changed the title of the Proposed Rule file to

   EO12866_SDWA NPDWR Perchlorate 2040-AF28 NPRM 20190305

3. I removed the first paragraph of the Tribal EO (see below) – which was the 1st paragraph in the old template. I did not change anything else in the body/text of the Tribal EO.

Executive Order 13175, entitled ''Consultation and Coordination with Indian Tribal Governments'' (65 FR 67249, November 9, 2000), requires the EPA to develop "an accountable process to ensure meaningful and timely input by Tribal officials in the development of regulatory policies that have Tribal implications." The definition of ''policies that have Tribal implications'' includes regulations that have "substantial direct effects on one or more Indian Tribes, on the relationship between the federal government and the Indian Tribes, or on the distribution of power and responsibilities between the federal government and Indian Tribes." Under Executive Order 13175, the EPA may not issue a regulation that has Tribal implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the federal government provides the funds necessary to pay the direct compliance costs incurred by Tribal governments, or the EPA consults with Tribal officials early in the process of developing the proposed regulation and develops a Tribal summary impact statement.

Please send me the final versions of the memos and I'll print them.

Sandy

From: Lousberg, Macara
Sent: Tuesday, March 05, 2019 7:22 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: e-files for the perchlorate pkg

Thanks Joe. Looping in Sandy.

Did you all get any comments from Anna or Lee?

Sent from my iPhone

Begin forwarded message:

From: "Tiago, Joseph" <Tiago.Joseph@epa.gov>
Date: March 5, 2019 at 5:27:53 PM EST
To: "Lousberg, Macara" <Lousberg.Macara@epa.gov>
Cc: "Burneson, Eric" <Burneson.Eric@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
Subject: FW: e-files for the perchlorate pkg

Hi Macara,

Please find attached the Perchlorate FRN package for review and processing. I'm bringing the hard copy of the package to you shortly.

Let me know if you have any questions.

Regards,

Joe.

MEMORANDUM

SUBJECT: *Federal Register* Notice Regarding the Proposed Rule for Perchlorate in Drinking Water for OMB Review (SAN 5555; RIN 2040-AD28)

FROM: David P. Ross
Assistant Administrator

TO: Brittany A. Bolen
Assistant Administrator

The Office of Water submits the National Primary Drinking Water Regulations: Proposed Perchlorate Rule and Economic analysis (SAN 5555; RIN 2040-AF28) to transmit to the Office of Management and Budget (OMB). This action contains a proposal to establish a Maximum Contaminant Level Goal (MCLG) of 0.056 mg/L and a National Primary Drinking Water Regulation for perchlorate that includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L. This action also includes proposed requirements for water systems to conduct monitoring and reporting on perchlorate and provide information on perchlorate to consumers. This action proposes requirements for primacy agencies that implement the public water system supervision program under SDWA. In addition, the proposal includes a list of treatment technologies to enable water systems to comply with the MCL including affordable technologies for small systems.

This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. Attached is "The Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation." This action also includes a request for comment on an alternative MCL/MCLG of 0.018 mg/L. Finally, because of the low levels of occurrence of perchlorate at the levels of concern, this action also requests comment on whether the EPA should withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

I recommend that OP transmit the attached Proposed Rule and Economic Analysis to the OMB for interagency review in accordance Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

1. Federal Register Notice
2. Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 4/12/2019 1:25:05 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: Perchlorate
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412 Redlinev5.docx

Lisa,

I have completed my review of the draft perchlorate rule and approve submission to OP for OMB review. The attached document contains my minor edits. Fantastic effort by you and your team to complete the requested revisions so quickly.

Thanks so much!
Jennifer

Message

From: Evalenko, Sandy [Evalenko.Sandy@epa.gov]
Sent: 3/6/2019 6:07:48 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]; Lousberg, Macara [Lousberg.Macara@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fields, Wanda [Fields.Wanda@epa.gov]
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg
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Subject: draft summary of perchlorate public comments
Attachments: Perchlorate Comment Summary V1.1.docx

Eric,
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Lisa Christ
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Office of Ground Water and Drinking Water
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- Association of Metropolitan Water Agencies
- National Rural Water Association
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- The Chlorine Institute
- California Farm Bureau Federation

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- Environmental Working Group
- Natural Resources Defense Council

These groups strongly disagree with EPA's rulemaking proposal and the suggested regulatory alternatives. All groups suggest that EPA should set a standard for Perchlorate in drinking water no higher than 2 µg/L. In addition, these stakeholders claim that EPA is not following the statutory requirements of SDWA in that the agency failed to consider an adequate margin of safety while establishing a protective public health MCLG.

Public Health Professional Organizations

American Academy of Pediatrics – Disagree with EPA's proposal and urges the agency to set the strongest possible MCLG for Perchlorate.

3. Organizations that are neutral

Association of State Drinking Water Administrators – The board has not taken a position on whether to regulate Perchlorate.

Message

From: Aguirre, Janita [Aguirre.Janita@epa.gov]
Sent: 5/23/2019 8:00:56 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: SIGNED: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (SAN 5555)
Attachments: Perchlorate Rule OW-19-000-5459.pdf

Way to go team! Congratulations!

Janita Aguirre – Special Assistant
U.S. Environmental Protection Agency | Office of Water
Phone: **(202) 566-1149** | Email: **aguirre.janita@epa.gov**

From: Pritchard, Eileen
Sent: Thursday, May 23, 2019 3:54 PM
To: Wheeler, Andrew <wheeler.andrew@epa.gov>; Jackson, Ryan <jackson.ryan@epa.gov>; Lyons, Troy <lyons.troy@epa.gov>; Bennett, Tate <Bennett.Tate@epa.gov>; White, Elizabeth <white.elizabeth@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Molina, Michael <molina.michael@epa.gov>; Best-Wong, Benita <Best-Wong.Benita@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; Ross, David P <ross.davidp@epa.gov>; Konkus, John <konkus.john@epa.gov>; Darwin, Henry <darwin.henry@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; McIntosh, Chad <mcintosh.chad@epa.gov>; Schiermeyer, Corry <schiermeyer.corry@epa.gov>
Cc: Wooden-Aguilar, Helena <Wooden-Aguilar.Helena@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>; Richardson, RobinH <Richardson.RobinH@epa.gov>; Hope, Brian <Hope.Brian@epa.gov>; Campbell, Ann <Campbell.Ann@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>; Sauerhage, Maggie <Sauerhage.Maggie@epa.gov>; Dennis, Allison <Dennis.Allison@epa.gov>; Wildeman, Anna <wildeman.anna@epa.gov>; McDonough, Owen <mcdonough.owen@epa.gov>; Pritchard, Eileen <Pritchard.Eileen@epa.gov>; Kime, Robin <Kime.Robin@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; DeBell, Kevin <debell.kevin@epa.gov>; Lovell, Will (William) <lovell.william@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Bowles, Jack <Bowles.Jack@epa.gov>; Benevento, Douglas <benevento.douglas@epa.gov>; Gaines, Cynthia <Gaines.Cynthia@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>; Sawyers, Andrew <Sawyers.Andrew@epa.gov>; Shimkin, Martha <Shimkin.Martha@epa.gov>; Kasat, Rakhi <Kasat.Rakhi@epa.gov>; Hackel, Angela <Hackel.Angela@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Subject: SIGNED: National Primary Drinking Water Regulations: Proposed Perchlorate Rule (SAN 5555)

Good Afternoon.

Today, the Administrator signed the proposed rule entitled, **"National Primary Drinking Water Regulations: Proposed Perchlorate Rule. (SAN 5555)."**

This rule proposes to solicit public comment on the EPA' s proposal to establish a national primary drinking water regulation (NPDWR) and a non-enforceable maximum contaminant level goal (MCLG) for perchlorate under the Safe Drinking Water Act (SDWA). The proposed NPDWR includes an enforceable maximum contaminant level (MCL) of 0.056 mg/L (56 µg/L), which is proposed to be set at a level equal to the proposed MCLG. The EPA is seeking comment in the attached notice on whether the Agency should consider setting the perchlorate MCLG and MCL at alternative values of0.018 mg/L (18 µg/L) and 0.090 mg/L (90 µg/L). The EPA is also seeking comment on whether it should withdraw the Agency's 2011 determination to regulate perchlorate in drinking water.

An additional extension was given for signature of the proposed rule until May 28, 2019. The EPA is addressing the consent decree requirements to sign a NPDWR and issue a MCLG for perchlorate in this proposed rule by May 28, 2019.

Attached is the signed and dated proposed rule. For your convenience, please go to **p. 146** for the Administrator's signature.

Please contact me if you have any questions regarding this email.

Eileen Pritchard
Special Assistant: Office of the Administrator
(202) 564-6578 (d)
pritchard.eileen@epa.gov

Message

From: Lousberg, Macara [Lousberg.Macara@epa.gov]
Sent: 3/6/2019 12:22:10 AM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]
CC: Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: Fwd: e-files for the perchlorate pkg
Attachments: Clean EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190305.docx; ATT00001.htm; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190301.docx; ATT00002.htm; Transmittal Memo AA to OPEI 3-5-19.docx; ATT00003.htm; Transmittal Memo EB to JM 3-5-19.docx; ATT00004.htm; Transmittal Memo JM to DR 3-5-19.docx; ATT00005.htm; Perchlorate Draft Action Memo 3-5-19_v1.docx; ATT00006.htm

Thanks Joe. Looping in Sandy.

Did you all get any comments from Anna or Lee?

Sent from my iPhone

Begin forwarded message:

> **From:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>
> **Date:** March 5, 2019 at 5:27:53 PM EST
> **To:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
> **Cc:** "Burneson, Eric" <Burneson.Eric@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Subject: FW: e-files for the perchlorate pkg**
>
> Hi Macara,
>
> Please find attached the Perchlorate FRN package for review and processing. I'm bringing the hard copy of the package to you shortly.
>
> Let me know if you have any questions.
>
> Regards,
>
> Joe.

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 4/2/2019 7:32:18 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN
Attachments: FRN Perchlorate Rule Redline for Review 4-2-19_LC.docx

Thanks Sam – my comments are attached.

From: Hernandez-Quinones, Samuel
Sent: Tuesday, April 02, 2019 9:01 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: DELIBERATIVE: Revised Perchlorate FRN

DELIBERATIVE

Hi,

Attached for your review is a redline version of the revised FRN for perchlorate.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Wadlington, Christina [Wadlington.Christina@epa.gov]
Sent: 5/23/2019 12:03:59 PM
To: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]
Attachments: NPDWR for the Proposed Perchlorate Rule.docx

Importance: High

Can you confirm that this is the version that is being signed that I need to post on the web?

From: Flaharty, Stephanie
Sent: Wednesday, May 22, 2019 3:15 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Thompkins, Anita <Thompkins.Anita@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Corr, Elizabeth <Corr.Elizabeth@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Zipf, Lynn <Zipf.Lynn@epa.gov>
Subject: NPDWR for the Proposed Perchlorate Rule Package [CMS Control #OW-19-000-5459]
Importance: High

Sandy,

This is to forward the NPDWR for the Proposed Perchlorate Rule package's electronic suite of files. As we discussed, Joe is on his way to Janita with the Action Memo for Dave to sign, so that when we hear from OMB, we can move the package right away. All files are in CMS, including the most current version of the FRN.

Thanks as always for your assistance in moving this forward !

Steph

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/2/2019 1:01:12 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: DELIBERATIVE: Revised Perchlorate FRN
Attachments: FRN Perchlorate Rule Redline for Review 4-2-19.docx

DELIBERATIVE

Hi,

Attached for your review is a redline version of the revised FRN for perchlorate.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 5/15/2019 9:38:01 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: DRAFT perchlorate proposal
Attachments: Draft Perchlorate HRRCA 2019-05-06 revised per OMB comments_rk9.docx; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190515.docx; EPA Responses to EO12886 Comments - FRN Perchlorate NPDWR 5-15-19.docx

INTERNAL DELIBERATIVE

Eric,
Attached are the following draft revised documents:
The HRRCA
FRN clean version
FRN track change/comment response version

The draft documents address EO 12866 review comments and the most recent edits from Jennifer.

Thanks,
Lisa

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 3/1/2019 9:59:55 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: Revised Perchlorate FRN
Attachments: Clean EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190301.docx; Redline EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190301.docx

Hi,

Attached is the revised FRN for the Proposed Perchlorate Rule. You will find a clean version with the revisions incorporated and a redline version which compares the edits made since OWs latest review in early February.

Let me know if you have any questions or need to incorporate additional edits.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 5/15/2019 8:04:30 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: FRN V1
Attachments: CLEAN for Review V1 - EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190515.v2.docx

Thank you all! My final comments are attached.

From: Christ, Lisa
Sent: Wednesday, May 15, 2019 1:03 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: FRN V1

INTERNAL DELIBERATIVE

Jennifer,
Attached is the revised perchlorate proposal (clean version) that incorporates the last revisions from Dave re: request for comment on the HA if we withdraw the reg det. OST has cleared the revised language and we are awaiting OGC concurrence.

We've checked spacing, formatting, etc. Let us know if you have questions or concerns.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Wednesday, May 15, 2019 12:50 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FRN V1 with updated Paragraph Spacing

Attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 12/21/2018 2:46:40 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Revised Version - Perchlorate FRN
Attachments: Version-Control Perchlorate Rule FRN 12-20-18.docx

Hi Eric,

Attached is the revised version of the Perchlorate FRN. We have addressed all of Jennifer's comments and suggested edits as well as incorporated revisions from the Team on the HRRCA, Health Effects and Occurrence sections.

We are due to receive comments by COB today from OGC and from OW. Let me know if you have any comments or questions.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Thursday, December 20, 2018 9:16 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: RE: Revised Version - Perchlorate FRN

Lisa:
Yesterday Dave Ross asked for a copy of the Perchlorate FRN. We can give him the same version that went to Lee. However if there is a revised version that addresses some of the "open items" we discussed with Jennifer on Monday, it would be good to send that revised version forward. Can you let me know if an updated version is available today?
Thanks
Eric

From: Christ, Lisa
Sent: Wednesday, December 12, 2018 2:11 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Version - Perchlorate FRN

Jennifer –
The attached revised FRN addressed your edits and most of your comments/questions. Also, a few additional edits from Eric and Rajiv. As suggested by Eric, some of your questions are "open items" to be addressed post-OW/OGC review.
Lisa

From: Mclain, Jennifer
Sent: Tuesday, December 11, 2018 5:52 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Version - Perchlorate FRN

Lisa,
I am so impressed by the quality of the proposal your team put together. The attached includes my edits and comments/questions. If it would be helpful for you all to sit down and go over some of the later, rather than trying to respond in comment bubbles, I'm happy to do that. I am not as well versed on this information as you all so I may have made edits or comments that are not appropriate. If that is the case, please ignore the edit and don't feel the need to explain why.
Thanks much,
Jennifer

From: Christ, Lisa
Sent: Friday, December 07, 2018 3:16 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: Revised Version - Perchlorate FRN

Hi Jennifer,
The attached perchlorate proposal addresses my comments and Eric's. We have some additional information we are working on to provide more context for the HRRCA section. This version is ready for your and OW/OGC review. We'll fold in our additional information in the next round of edits.

Let us know if you have questions or concerns.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, December 07, 2018 3:10 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Version - Perchlorate FRN

Hi Lisa,

Attached is the revised FRN for Perchlorate.

Thanks

Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 5/21/2019 6:35:05 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Nickerson, William [Nickerson.William@epa.gov]
Subject: Draft working version Perchlorate FRN
Attachments: 2-30pm Ver 5-21 EPA Responses to EO12886 Comments - FRN Perchlorate NPDWR Rd 2.docx

Draft working version is attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Sent: 3/5/2019 3:13:25 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: IO's consolidated comments: Transmittal Memos for Perchlorate
Attachments: Transmittal Memo JM to DR 3-4-19 ytg+jm.docx; Perchlorate Draft Action Memo 3-4-19.ytg.docx

Hi Eric

Apologies for the multiple emails on these memos. Attached please find IO's comments on two documents – the transmittal memo from JM to DR and one from DR to Wheeler.

For ease of making the corrections, in the JM to DR memo (first attachment), I consolidated the comments from last night and this morning all into this document (in addition to correcting the typo in the "From" and "To"). Please apply the edits to other memos as well (i.e., EB to JM, JM to DR, and AA to OPEI). The second attachment contains edits to the DR to Wheeler memo. Please note the comment boxes that ask the team to double check some of the numbers.

Please let me know if you have any questions or concerns with any of the edits. Thank you!

Yu-Ting Guilaran, P.E.
Acting Deputy Office Director
Office of Ground Water and Drinking Water
Office of Water
U.S. Environmental Protection Agency

Tel: 202-564-6591

From: Guilaran, Yu-Ting
Sent: Tuesday, March 5, 2019 8:11 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Transmittal Memos for Perchlorate

Hi Eric
I understand that Jennifer provided additional comments on the memos yesterday evening. Additionally, please make the following edits in all transmittal memos per the excerpted redline-strikeout below, thank you.

"This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs. This action also includes a requests for comment an alternative MCL/MCLG of .018 mg/L. Finally, because of the low levels of occurrence of perchlorate at the levels of concern, this action also requests comment on whether the EPA should withdraw its determination to regulate perchlorate. Under this alternative, there would be no MCLG or national primary drinking water regulation for perchlorate.

I recommend that you transmit the attached notice to the Office of Policy for ~~Inter Agency Review~~ interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Yu-Ting Guilaran, P.E.
Acting Deputy Office Director
Office of Ground Water and Drinking Water
Office of Water
U.S. Environmental Protection Agency

Tel: 202-564-6591

From: Guilaran, Yu-Ting
Sent: Monday, March 4, 2019 5:14 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Transmittal Memos for Perchlorate

Eric
Please see minor grammatical/space edits in track changes in the attached. These edits apply to the other memos as well. Please let me know if you have any questions. Thanks.

Yu-Ting Guilaran, P.E.
Acting Deputy Office Director
Office of Ground Water and Drinking Water
Office of Water
U.S. Environmental Protection Agency

Tel: 202-564-6591

From: Burneson, Eric
Sent: Monday, March 4, 2019 2:15 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: Transmittal Memos for Perchlorate

Jennifer and Yu-Ting:
Attached for your review and comment are the transmittal memos we are preparing to facilitate Inter Agency Review of the propose perchlorate drinking water standard. We will be preparing the "blue folder"package to facilitate getting these documents to the Office of Policy for transmission to OMB for review. Please note that we have been informed that OGC concurrence requires senior level approval now and we do not expect to receive that concurrence today. Also a reminder that the Action memo is a draft at this stage of the process to identify the information we intend to highlight for the Administrator when it is transmitted for signature after OMB concludes Inter Agency Review.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water

U.S. Environmental Protection Agency
202 564 5250

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/5/2019 7:57:12 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg
Attachments: Perchlorate Draft Action Memo 4-5-19.docx; Transmittal Memo AA to OPEI 4-5-19.docx; Transmittal Memo EB to JM 4-5-19.docx; Transmittal Memo JM to DR 4-5-19.docx

Revised Memorandums attached.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Friday, April 05, 2019 1:47 PM
To: Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg

Perchlorate team
Can we review and revise to be made to the other parts of this package to be consistent with the revised notice.
Thanks

From: Mclain, Jennifer
Sent: Friday, April 05, 2019 12:28 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg

Eric – is your team working on any updates to the package that may be needed to incorporate the changes we made to the draft proposed rule?

From: Tiago, Joseph
Sent: Wednesday, March 06, 2019 1:32 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Hi Sandy,

Thank you for your edits. Your changes have been accepted and two typos corrected as follows:

DR to AW Memo:
Under Impacts: ...and administration requirements consisted of the majority of the annual cost.

DR to BB Memo:
This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs.

Let me know if you have any questions.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 1:08 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

I think you mean the NPRM – the rule is attached.
If not, let me know.
Sandy

From: Tiago, Joseph
Sent: Wednesday, March 06, 2019 1:05 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Thanks, Sandy!

Note the EO 12866 file is blank – not sure it was intentional.

We'll get you a revised version of the memos.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 12:59 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: Use this version - Comments: e-files for the perchlorate pkg
Importance: High

In this version, I also added the San and Rin in the subject line for the Transmittal memo.

Thanks for sending the Perchlorate package. I have a few edits/comments.

1. Thank you for preparing both a transmittal memo and draft action memo. Attached are comments and suggestions.

2. A minor edit regarding the NPRM file name and OMB's requirements. OMB is particular regarding the naming convention. I added the title to the first page of the FRN and changed the title of the Proposed Rule file to

   EO12866_SDWA NPDWR Perchlorate 2040-AF28 NPRM 20190305

3. I removed the first paragraph of the Tribal EO (see below) – which was the 1st paragraph in the old template. I did not change anything else in the body/text of the Tribal EO.

Executive Order 13175, entitled "Consultation and Coordination with Indian Tribal Governments" (65 FR 67249, November 9, 2000), requires the EPA to develop "an accountable process to ensure meaningful and timely input by Tribal officials in the development of regulatory policies that have Tribal implications." The definition of "policies that have Tribal implications" includes regulations that have "substantial direct effects on one or more Indian Tribes, on the relationship between the federal government and the Indian Tribes, or on the distribution of power and responsibilities between the federal government and Indian Tribes." Under Executive Order 13175, the EPA may not issue a regulation that has Tribal implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the federal government provides the funds necessary to pay the direct compliance costs incurred by Tribal governments, or the EPA consults with Tribal officials early in the process of developing the proposed regulation and develops a Tribal summary impact statement.

Please send me the final versions of the memos and I'll print them.

Sandy

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To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: e-files for the perchlorate pkg

Thanks Joe. Looping in Sandy.

Did you all get any comments from Anna or Lee?

Sent from my iPhone

Begin forwarded message:

> **From:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>
> **Date:** March 5, 2019 at 5:27:53 PM EST
> **To:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
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>
> Hi Macara,
>
> Please find attached the Perchlorate FRN package for review and processing. I'm bringing the hard copy of the package to you shortly.
>
> Let me know if you have any questions.

Regards,

Joe.

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 4/5/2019 4:28:00 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg
Attachments: Perchlorate Draft Action Memo .SE.3-5-19_v1_OGWDW_030619.docx; Transmittal Memo AA to OPEI. SE.3-5-19_OGWDW_030619.docx; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190305.docx

Eric – is your team working on any updates to the package that may be needed to incorporate the changes we made to the draft proposed rule?

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Please send me the final versions of the memos and I'll print them.

Sandy

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Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer

<Mclain.Jennifer@epa.gov>
Subject: Fwd: e-files for the perchlorate pkg

Thanks Joe. Looping in Sandy.

Did you all get any comments from Anna or Lee?

Sent from my iPhone

Begin forwarded message:

> **From:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>
> **Date:** March 5, 2019 at 5:27:53 PM EST
> **To:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
> **Cc:** "Burneson, Eric" <Burneson.Eric@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Subject: FW: e-files for the perchlorate pkg**
>
> Hi Macara,
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>
> Let me know if you have any questions.
>
> Regards,
>
> Joe.

Message

From: Huff, Lisa [Huff.Lisa@epa.gov]
Sent: 5/17/2019 5:20:56 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Action Needed: Perchlorate Memos-
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190412.docx; ATT00001.htm; Transmittal Memo JM to DR 4-9-19.docx; ATT00002.htm; Perchlorate Draft Action Memo 4-9-19.docx; ATT00003.htm; image2019-04-12-134922.pdf; ATT00004.htm; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx; ATT00005.htm

Importance: High

Sam,
Please see note below from Steph re: getting the package together ASAP – do we expect the memos to change at all? Other than modifying the memos for signature? Can you put together the package and make sure the signature

Thanks,
Lisa

From: Burneson, Eric
Sent: Friday, May 17, 2019 12:05 PM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Subject: FW: Action Needed: Perchlorate Memos-
Importance: High

From: Flaharty, Stephanie
Sent: Friday, May 17, 2019 12:04 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Huff, Rebecca <huff.rebecca@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Corr, Elizabeth <Corr.Elizabeth@epa.gov>
Subject: Action Needed: Perchlorate Memos-
Importance: High

All,

OMB review for Perchlorate is projected to end Monday or Tuesday at the latest. The package will need to fly through here for AO signature by 5/28 (Tuesday after Memorial Day).

Sandy has been asked to get as much of the package ready as possible. She's asked us to modify the memos for the signature package (with a placeholder for OMB's review in the Action Memo).

Can we assume the memos will not change significantly at this point? If we do need to revise them, can you start on it today?

Thanks!
Steph

From: Evalenko, Sandy
Sent: Friday, May 17, 2019 11:31 AM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Corr, Elizabeth <Corr.Elizabeth@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: heads up: Revised Perchlorate FRN and related items (to go TO OP today

Steph/Elizabeth: Do you have the revised memos for the Perchlorate? I need to have them reviewed quickly.

From: Evalenko, Sandy
Sent: Friday, April 12, 2019 1:57 PM
To: Nurse, Leanne <Nurse.Leanne@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Subject: heads up: Revised Perchlorate FRN and related items (to go TO OP today

Leanne: attached are revised documents for the NPDWR Perchlorate norm (San 5555). I've copied Macara Lousberg and she has received verbal clearance from Lee Forsgren to move this forward OP for OMB review. Please call me at 202-297-8108 if you have questions.
Sandy

Sent from my iPhoneu have

Begin forwarded message:

> **From:** "Corr, Elizabeth" <Corr.Elizabeth@epa.gov>
> **Date:** April 12, 2019 at 1:45:02 PM EDT
> **To:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>, "Evalenko, Sandy" <Evalenko.Sandy@epa.gov>, "Brown, Sineta" <Brown.Sineta@epa.gov>, "Fields, Wanda" <Fields.Wanda@epa.gov>
> **Cc:** "Flaharty, Stephanie" <Flaharty.Stephanie@epa.gov>, "Christ, Lisa" <Christ.Lisa@epa.gov>, "Wadlington, Christina" <Wadlington.Christina@epa.gov>
> **Subject: Revised Perchlorate FRN and related items (to go TO OP today**
>
> HRRCA, transmittal, action memo, pdf of Jennifer's signature, and FRN. Pls let us know if anything else is needed to get the package to OP today. (I will be here til 3 PM.)
> Many thanks.
>
> ---
>
> **From:** Christ, Lisa
> **Sent:** Friday, April 12, 2019 11:38 AM
> **To:** Corr, Elizabeth <Corr.Elizabeth@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
> **Cc:** Tiago, Joseph <Tiago.Joseph@epa.gov>
> **Subject:** FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos
>
> FYI ---
>
> ---
>
> **From:** Christ, Lisa
> **Sent:** Friday, April 12, 2019 10:52 AM
> **To:** Mclain, Jennifer <Mclain.Jennifer@epa.gov>
> **Cc:** Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <khera.rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
> **Subject:** FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi Jennifer,
Attached for your transmittal to OW are the following:
The FRN for the NPDWR for Perchlorate, proposed rule (a clean and a track changes version for convenience)
Health Risk Reduction Cost Analysis
Transmittal/Action memos

Let us know if you need anything else.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, April 12, 2019 10:44 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi,

Attached are the revised clean versions of the Perchlorate FRN and HRRCA, which incorporate all the suggested edits to date (4-12-19).

Here also you will find a revised redline version which incorporates all edits and changes to the document made to the FRN since the last OW-IO review (3-11-19).

Finally, attached are the most recent version of the corresponding transmittal memos.

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Evalenko, Sandy [Evalenko.Sandy@epa.gov]
Sent: 3/8/2019 5:18:22 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Fields, Wanda [Fields.Wanda@epa.gov]
CC: Lousberg, Macara [Lousberg.Macara@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: Use this version - Comments: e-files for the perchlorate pkg
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190308.docx

Sam: Thanks so much for the final version. Here's your final version with the standard OMB naming convention. I did not change anything but the title of the electronic file.

Wanda: Please add this version to CMS.

Thanks,
Sandy

From: Hernandez-Quinones, Samuel
Sent: Friday, March 08, 2019 11:50 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Hi,

Attached is the revised version of the FRN which incorporates edits suggested by David Ross. We also updated a footnote and fixed a typo.

Thanks
Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Friday, March 08, 2019 11:41 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Thanks Sandy: Sam is incorporating Dave's edits and making a final edit to a footnote typo. He will send the revised to you shortly.
Eric

From: Evalenko, Sandy
Sent: Friday, March 08, 2019 9:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Eric: This is the right version (148 pages). I recommended a few edits to the EO section that removed text. The original NPRM submitted in the blue folder was 152 pages.

Once Wanda makes a pdf of the Transmittal memo, I'll forward the rule to OP for OMB review and copy you all.

Sandy

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Sent: Friday, March 08, 2019 9:00 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg

Team: Please use the attached files to make the edits that Dave requested in his email last night.

Sandy and Macara : can you please confirm the attached is the latest version you are working with?

From: Evalenko, Sandy
Sent: Wednesday, March 06, 2019 1:08 PM
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If not, let me know.
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Thanks, Sandy!

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We'll get you a revised version of the memos.

Joe.

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Did you all get any comments from Anna or Lee?

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CC: Lousberg, Macara [Lousberg.Macara@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
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Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190308v1.docx

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Thanks
Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Friday, March 08, 2019 11:41 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Thanks Sandy: Sam is incorporating Dave's edits and making a final edit to a footnote typo. He will send the revised to you shortly.
Eric

From: Evalenko, Sandy
Sent: Friday, March 08, 2019 9:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Eric: This is the right version (148 pages). I recommended a few edits to the EO section that removed text. The original NPRM submitted in the blue folder was 152 pages.

Once Wanda makes a pdf of the Transmittal memo, I'll forward the rule to OP for OMB review and copy you all.

Sandy

From: Burneson, Eric
Sent: Friday, March 08, 2019 9:00 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg

Team: Please use the attached files to make the edits that Dave requested in his email last night.

Sandy and Macara : can you please confirm the attached is the latest version you are working with?

From: Evalenko, Sandy
Sent: Wednesday, March 06, 2019 1:08 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

I think you mean the NPRM – the rule is attached.
If not, let me know.
Sandy

From: Tiago, Joseph
Sent: Wednesday, March 06, 2019 1:05 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Thanks, Sandy!

Note the EO 12866 file is blank – not sure it was intentional.

We'll get you a revised version of the memos.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 12:59 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: Use this version - Comments: e-files for the perchlorate pkg
Importance: High

In this version, I also added the San and Rin in the subject line for the Transmittal memo.

Thanks for sending the Perchlorate package. I have a few edits/comments.

1. Thank you for preparing both a transmittal memo and draft action memo. Attached are comments and suggestions.

2. A minor edit regarding the NPRM file name and OMB's requirements. OMB is particular regarding the naming convention. I added the title to the first page of the FRN and changed the title of the Proposed Rule file to

   EO12866_SDWA NPDWR Perchlorate 2040-AF28 NPRM 20190305

3. I removed the first paragraph of the Tribal EO (see below) – which was the 1st paragraph in the old template. I did not change anything else in the body/text of the Tribal EO.

Executive Order 13175, entitled "Consultation and Coordination with Indian Tribal Governments" (65 FR 67249, November 9, 2000), requires the EPA to develop "an accountable process to ensure meaningful and timely input by Tribal officials in the development of regulatory policies that have Tribal implications." The definition of "policies that have Tribal implications" includes regulations that have "substantial direct effects on one or more Indian Tribes, on the relationship between the federal government and the Indian Tribes, or on the distribution of power and responsibilities between the federal government and Indian Tribes." Under Executive Order 13175, the EPA may not issue a regulation that has Tribal implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the federal government provides the funds necessary to pay the direct compliance costs incurred by Tribal governments, or the EPA consults with Tribal officials early in the process of developing the proposed regulation and develops a Tribal summary impact statement.

Please send me the final versions of the memos and I'll print them.

Sandy

From: Lousberg, Macara
Sent: Tuesday, March 05, 2019 7:22 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: e-files for the perchlorate pkg

Thanks Joe. Looping in Sandy.

Did you all get any comments from Anna or Lee?

Sent from my iPhone

Begin forwarded message:

> **From:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>
> **Date:** March 5, 2019 at 5:27:53 PM EST
> **To:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
> **Cc:** "Burneson, Eric" <Burneson.Eric@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Subject: FW: e-files for the perchlorate pkg**
>
> Hi Macara,
>
> Please find attached the Perchlorate FRN package for review and processing. I'm bringing the hard copy of the package to you shortly.

Let me know if you have any questions.

Regards,

Joe.

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 3/8/2019 3:03:40 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: Perchlorate
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190308.docx

Hi,

Here is the revised FRN which incorporates the suggested edits. We removed the broken references, updated the HHS consultation language, and updated the wage rate.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Friday, March 08, 2019 9:58 AM
To: Khera, Rajiv <Khera.Rajiv@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>
Subject: Re: Perchlorate

Thanks Rajiv
Let's get the FRN corrected on this wage rate as well and run a quick check on the other numbers in the EA section

Sent from my iPhone

On Mar 8, 2019, at 9:22 AM, Khera, Rajiv <Khera.Rajiv@epa.gov> wrote:

> Hi Eric-
> The system-weighted average wage rate in the perchlorate rule is $34.71 (see appendix C of HRRCA for derivation). The incorrect value is a relic of a system-weighted average of old wage rates, which are lower than the $2017 WBS wage rates. I don't know how it got into the FRN. The technical and managerial input labor costs (in $2017) are based on the 2006 CWSS wage question and a benefits multiplier based on Bureau of Labor Statistics total compensation rates. Our labor cost report was externally peer reviewed. We have been escalating total compensation using "Total compensation for Private industry workers in Utilities, Index, CIU2014400000000I (B)". Thanks
> Rajiv

From: Burneson, Eric
Sent: Friday, March 08, 2019 7:28 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Fwd: Perchlorate

See below for Dave's comments. Note that overall he is happy with the notice.
Rajiv can you get me the source for the operators hourly rate and the breakdown what fully loaded means?

Sent from my iPhone

Begin forwarded message:

> **From:** "Ross, David P" <ross.davidp@epa.gov>
> **Date:** March 7, 2019 at 9:36:54 PM EST
> **To:** "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>
> **Cc:** "Wildeman, Anna" <wildeman.anna@epa.gov>, "Forsgren, Lee" <Forsgren.Lee@epa.gov>, "McDonough, Owen" <mcdonough.owen@epa.gov>, "Kramer, Jessica L." <kramer.jessical@epa.gov>, "Mejias, Melissa" <mejias.melissa@epa.gov>, "Aguirre, Janita" <Aguirre.Janita@epa.gov>
> **Subject: Perchlorate**
>
> Hi there. I'm flipping through the preamble right now and paused in the Econ analysis. We think the fully loaded hourly rate for water systems is 29.60/hour? Fully loaded?
>
> I'm going to sign the memo to Brittany to keep this moving on schedule. But on page 74, check the error code embedded in the first full paragraph. I'm sure we can clean this up during OMB review, but try to give this a quick flip to cut down on the OMB pass back stuff. We also have an open item comment on page 112 that says we should update language before it goes to OMB.
>
> Also, when we publish this for public comment, I expect us to include copies of our references beginning on page 113 in the docket so that everyone has ready access to them. I believe in full transparency and making life easier on all commenters. Thanks.
>
> Overall, I'm comfortable with the proposal and appreciate the hard work on this. Thanks to both of you and team.
>
> Dave
>
> Sent from my iPhone

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/4/2019 9:45:52 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: Revised Perchlorate FRN
Attachments: FRN Perchlorate Rule Redline for Review 4-4-19 SHQ.docx

Hi Eric,

Here is the redline document. Let me know if this one is working correctly.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Thursday, April 04, 2019 5:15 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Perchlorate FRN

Sam: I am having problem with the track changes document similar to the problems I had yesterday with Dawn's comments. It opens as a blank document. Can you please resend?
Thanks
Eric

From: Hernandez-Quinones, Samuel
Sent: Thursday, April 04, 2019 3:23 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Perchlorate FRN

Hi Eric,

The team has completed the revisions to the Perchlorate FRN. Attached are two copies a redline that compares the updated document to the document that OW developed on 3/11/19. There is also a clean copy ready to be submitted to OP which adheres to the formatting guidelines.

If you have any comments or edits, please let me know so that such changes can be incorporated into the controlled version.

Thanks
Sam

==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 3/4/2019 11:25:05 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: Revised Perchlorate Documents 3-4-19
Attachments: Clean EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190301.pdf; EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190301.pdf

Hi Eric,

FYI, here are copies of the latest version of the FRN and the HRRCA for Perchlorate.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/4/2019 4:45:28 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: FW: DELIBERATIVE: Revised Perchlorate FRN
Attachments: FRN Perchlorate Rule Redline for Review 4-3-19SHQ-V1.jlm2.docx

Hi Eric,

I am currently incorporating Jennifer's suggested edits as well as the new table.

I am having some formatting issues, but as soon as I am done I will forward the revised FRN to you.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Mclain, Jennifer
Sent: Thursday, April 04, 2019 12:05 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Perchlorate team – Great job in incorporating a second alternative MCLG/MCL and this new information on IQ. My edits are in the attached. Two primary points:

- I think it would be helpful to clarify that we are assessing a decrement in population IQ vs. individual IQ. I added it in a few places in the attached (although you may determine a better way to do this).
- Table III-2: The title now includes the 3% decrease but the table does not?

Please let me know if you have any questions.

Jennifer

From: Burneson, Eric
Sent: Wednesday, April 03, 2019 2:40 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel

<Hernandez.Samuel@epa.gov>
Subject: FW: DELIBERATIVE: Revised Perchlorate FRN

Jennifer:
Attached please find a revised proposed NPDWR for perchlorate. Note that we are making an additional adjustment to Table III-2 to reflect the 3 IQ point decrement. We would appreciate your review and comment as soon as possible.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel
Sent: Wednesday, April 03, 2019 2:31 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Hi Eric,

Attached is the revised redline document. We are still waiting for one revision on Table III-2 which we should have ready later today. All the other requested edits have been incorporated. Once we receive any comments from Jenifer (if applicable) I will send a revised clean copy to all.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Tuesday, April 02, 2019 4:03 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Attached please find my comments. Please note that in the POD section I am asking if we can included the standard error for individual IQ tests. It looks as though one of the documents we reference includes this value but does not state what the standard error is. If we cannot find a reference for the standard error related to IQ tests we should delete the text I am suggesting we add.

I have attempted to add more rationale for our selection of the proposed MCLG and also added specific requests for comment about our methodology for deriving the MCLG.

Thank you for preparing this revised draft so quickly. Please let me know if you have questions. I have alerted Jennifer and she expects a revised draft tomorrow. Please let me know if that is not possible.
Eric

From: Christ, Lisa
Sent: Tuesday, April 02, 2019 3:32 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: DELIBERATIVE: Revised Perchlorate FRN

Thanks Sam – my comments are attached.

From: Hernandez-Quinones, Samuel
Sent: Tuesday, April 02, 2019 9:01 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: DELIBERATIVE: Revised Perchlorate FRN

DELIBERATIVE

Hi,

Attached for your review is a redline version of the revised FRN for perchlorate.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Messier, Dawn [Messier.Dawn@epa.gov]
Sent: 1/29/2019 10:50:38 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: OGC staff comments on draft perchlorate proposed rule
Attachments: Perchlorate Rule FRN 12-12-18-cleanDMMcom1-29-19.docx

Attached. Please let me know if you have any questions. As discussed, I am planning to look at this again while it is with the workgroup. Also, I'd like to discuss the anticipated schedule for OGC management review when you get a chance.

As always… a well-written product that was easy to comment on. Thanks!!!!! Dawn

Dawn Messier
U.S.E.P.A.
Office of General Counsel
Water Law Office
202-564-5517

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 10/3/2018 7:07:34 PM
To: Bretz, Emily (USANYS) [Emily.Bretz@usdoj.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; robert.yalen@USDOJ.GOV; Messier, Dawn [Messier.Dawn@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: did we get comments during the perchlorate peer review process from NRDC?
Attachments: TO 22 Public Comment Report Final.pdf; Perchlorate Public Comment Report_Panel 2.pdf

FYI

From: Hernandez-Quinones, Samuel
Sent: Wednesday, October 03, 2018 3:02 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: did we get comments during the perchlorate peer review process from NRDC?

Hi Lisa,

We got comments from NRDC during the public comment period on both Panel 1&2 of the perchlorate peer review. You can see the comments in Page# 125 (1st Panel) and Page# 79 (2nd Panel).

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa
Sent: Wednesday, October 03, 2018 2:42 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: did we get comments during the perchlorate peer review process from NRDC?

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Public Comment Summary Report for EPA's Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

EPA Contract No. EP-C-13-010
Task Order No. 2015-022

January 2, 2018

Prepared for:
U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
Standards and Risk Management Division
1200 Pennsylvania Avenue, NW (MC 4304T)
Washington DC 20460

Prepared by:
Versar, Inc.
6850 Versar Center
Springfield, VA 22151

I. INTRODUCTION

Versar, Inc. (Versar) is an EPA contractor charged with coordinating the external peer review of EPA's draft document entitled "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (Draft MCLG Approaches Report). As part of the peer review process, EPA published a Federal Register Notice (82 FR 43354) on September 15, 2017 to announce the release of the materials for public comment. The original 45-day public comment period ended on October 30, 2017, but the public comment period was extended an additional 21 days to November 20, 2017. Supporting documentation, including the draft charge questions that will be addressed by the peer reviewers, was also made publicly available in a companion Federal Register Notice.

The purpose of this document is to provide a brief overview of the public comments on EPA's "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water," as submitted to EPA's public docket (Docket ID No. EPA-HQ-OW-2016-0438). The public comments which are technical in nature are included with this report in their entirety (Attachment 1). All comments are also available for download from the Federal docket (*http://www.regulations.gov*).

II. PUBLIC COMMENT OVERVIEW

A total of 17 comments/submissions were uploaded to the docket, however, only 11 of these submissions contained technical comments on the Draft MCLG Approaches Report. Of the six remaining comments, one submission was from a concerned resident in California (Mr. Larry Ladd) who was expressing gratitude for the action, three submissions (from the Association of Metropolitan Water Agencies, Perchlorate Study Group, and The Chlorine Institute) were a request for an extension to the public comment period, and two submissions were submitted anonymously that were considered off-topic.

The following 11 organizations/individuals submitted technical comments on the Draft MCLG Approaches Report:

- American Chemistry Council
- American Water Works Association / Ramboll Environ US Corporation / ScitoVation
- Association of Metropolitan Water Agencies
- The Chlorine Institute
- Department of Defense
- Environmental Defense Fund / Natural Resources Defense Council
- Environmental Working Group
- NASA
- Perchlorate Study Group / Intertox, Inc.
- The US Conference of Mayors
- Western Growers

ED_005043_00062727-00002

Table 1 below provides the number of pages for each technical submittal, and a list of topics covered in each. Overall, the comments discussed:

Background science: hypothyroxinemia for MCLG setting, mechanism of action, main source of perchlorate, thyroid hormone biology, citations, confounders (other goitrogens), improve clarity/transparency, Executive Summary, use of T4 instead of TSH, hypothyroxinemia for MCLG setting, risk of bias – Lit Review, perchlorate occurrence, iodine deficiency vs. perchlorate, neurodevelopmental tests, measurement of fT4, significance of effect, uncertainties – neurodevelopment, fT4 in later gestation, perchlorate and IQ, other health effects;

BBDR model: confounders (other goitrogens), improve clarity/transparency, model uncertainty, hCG, NIS Km, perchlorate impact on fT4 and thyroid hormones, plasma protein binding, model precision, rest of body compartment, significance of effect, TSH T4 set point, uncertainty and sensitivity analysis, updated Lumen model, use of T4 instead of TSH, model output, low iodine predictions, model validation, hypothyroxinemia for MCLG setting, additional unaccounted for sensitive population, model accuracy, extending the model to early pregnancy, T4 production rate, epidemiology data used in the model, animal studies, incorporation of the TSH feedback loop, limited data on toxicokinetics and toxicodynamics of perchlorate, variable expression of the NIS gene, failure to address compensation and adaptation, TSH feedback loop, limiting model to 1st trimester), inherent conservatism, weak TSH response, deriving the distribution of fT4, mechanism of action, uncertainty factors;

Literature Review: Risk of possible bias, improve clarity/transparency, peer review, animal studies, confounders, misclassification of studies, fT4 measurement, systematic review, neurodevelopment outcomes, utilization of Group 2 and Group 3 papers, neurodevelopment endpoint selection, hypothyroxinemia;

Analytical approach – connect to neurodevelopment with Epi: process to calculate MCLG, presentation of conclusions, uncertainties – digitization of figures, improve clarity/transparency, confounders, inherent conservatism, use of fT4 to connect to neurodevelopment, significance of effect; Finken et al., uncertainties – population evaluated, definition of hypothyroxinemia, suggested endpoint for rulemaking, risk of possible bias, high TH and neurodevelopment, confounding, single thyroid hormone measurement, uncertainties – fT4 and neurodevelopment, uncertainties - iodine intake level, uncertainties within the model, approaches, and/or studies, uncertainties – sample size, uncertainties – neurodevelopmental tests;

Analytical approach – deriving fT4 distribution: improve clarity/transparency, shape of distributions, and determining distribution of fT4;

Analytical approach – Appendix Approach: relevance of Steinmaus et al. analysis, baseline used in analysis, improve clarity/transparency, uncertainty in effect estimate, relevance of Korevaar analysis, clinical significance of effect;

Analytical approach – shifting hX dist: improve clarity/transparency, hypothyroxinemia for MCLG setting, significance of effect; hX percentile cut off;

General Comments: uncertainty factor, improve clarity/transparency, executive summary, inherent conservatism, reference dose, uncertainties within the model, approaches, and/or studies, confounders (other goitrogens), hypothyroxinemia, iodine deficiency vs. perchlorate, relative source contribution, other health effects, perchlorate impact on thyroid hormones, overall approach.

Table 1. Summary of Technical Related Public Comments Submitted to Docket EPA-HQ-OW-2016-0438

No. of Pages	Topics covered
American Chemistry Council	
5 pages	• General comments: o Improve clarity/transparency o Executive summary o Hypothyroxinemia o Inherent conservatism • Background science: o Significance of effect o Uncertainties – neurodevelopment
American Water Works Association (including comments prepared by Ramboll Environ US Corporation and ScitoVation)	
21 pages	• BBDR model: o Extending the Model to early pregnancy o hCG o Model accuracy o Improve clarity/transparency o Model validation o Model precision o NIS Km o Perchlorate impact on thyroid hormones o T4 production rate • Literature review: o Improve clarity/transparency o Confounders o Systematic review o Neurodevelopmental outcomes o Utilization of Group 2 and Group 3 papers o Possible risk of bias • Analytical approach – connect to neurodevelopment with Epi: o Definition of hypothyroxinemia o Uncertainties – Population evaluated o Confounders • Background science: o Measurement of fT4
Association of Metropolitan Water Agencies	
10 pages	• BBDR model: o Confounding o Limiting BBDR model to 1st trimester o Low iodine predictions o Perchlorate impact on thyroid hormones o TSH feedback loop • General Comments:

Table 1. Summary of Technical Related Public Comments Submitted to Docket EPA-HQ-OW-2016-0438

No. of Pages	Topics covered
	○ Iodine deficiency vs. perchlorate ○ Relative source contribution ○ Other health effects ○ Perchlorate impact on thyroid hormones • Analytical approach – connect to neurodevelopment with Epi: ○ High TH and neurodevelopment ○ Confounding ○ Single thyroid hormone measurement ○ Uncertainties – fT4 and neurodevelopment ○ Uncertainties – iodine intake level ○ Uncertainties – population evaluated ○ Significance of effect; Finken et al. ○ Uncertainties within the model, approaches, and/or studies ○ Uncertainties – sample size ○ Uncertainties – neurodevelopmental tests • Background science: ○ fT4 in later gestation ○ Perchlorate and IQ • Literature review: ○ Risk of possible bias ○ Hypothyroxinemia • Analytical approach – shifting hX dist: ○ hX percentile cut off
The Chlorine Institute	
9 pages	• BBDR model: ○ Confounders (other goitrogens) ○ Epidemiology data used in the model ○ Animal studies ○ Incorporation of the TSH feedback loop ○ Limited data on toxicokinetics and toxicodynamics of perchlorate ○ Model validation ○ Precision of the model ○ Model output ○ Variable expression of the NIS gene ○ Failure to address compensation and adaptation • Analytical approach – connect to neurodevelopment with Epi: ○ Risk of possible bias • Literature review: ○ Neurodevelopmental endpoint selection ○ Animal studies • Analytical approach – deriving fT4 distribution: ○ Determining distribution of fT4 • Analytical approach – shifting hX dist: ○ Significance of effect • Analytical approach – Appendix Approach: ○ Relevance of Steinmaus et al. ○ Significance of effect

Table 1. Summary of Technical Related Public Comments Submitted to Docket EPA-HQ-OW-2016-0438

No. of Pages	Topics covered
Department of Defense	
17 pages	• BBDR model: o hCG o Improve clarity/transparency o NIS Km o Perchlorate impact on fT4 o Plasma protein binding o Precision of the model o Rest of body compartment o Significance of effect o TSH T4 set point o Uncertainty and sensitivity analysis o Updated Lumen model o Use of T4 instead of TSH o Model output • Analytical approach – deriving fT4 distribution: o Improve clarity/transparency o Shape of distribution • Background science: o Mechanism of action o Main source of perchlorate o Thyroid hormone biology o Citations o Confounders (other goitrogens) o Improve clarity/transparency o Executive Summary o Use of T4 instead of TSH o Hypothyroxinemia for MCLG setting o Risk of bias – Lit Review o Other health effects • Literature review: o Risk of possible bias o Improve clarity/transparency • Analytical approach – Connect to neurodevelopment with Epi: o Process to calculate the MCLG o Presentation of conclusions • Analytical approach – Appendix Approach: o Relevance of Steinmaus et al. analysis o Baseline used in analysis o Improve clarity/transparency o Uncertainty in effect estimate o Relevance of Korevaar analysis o Clinical significance of effect
Environmental Defense Fund/Natural Resources Defense Council	
6 pages	• BBDR model: o Low iodine o Confounders (other goitrogens) o Uncertainty factors • General Comments: o Uncertainty factor

Table 1. Summary of Technical Related Public Comments Submitted to Docket EPA-HQ-OW-2016-0438

No. of Pages	Topics covered
Environmental Working Group (EWG)	

4 pages	• BBDR Model:
	  o Additional unaccounted for sensitive population
	• General Comments:
	  o Confounders (other goitrogens)
	  o Overall approach
	  o Uncertainty factor
	  o Reference dose
	• Analytical approach – Connect to neurodevelopment with Epi:
	  o Suggested endpoint for rulemaking

NASA	

7 pages	• BBDR Model:
	  o Model validation
	• General Comments:
	  o Uncertainties within the Model, Approaches and/or Studies
	• Literature Review:
	  o Improve clarity/transparency
	  o Risk of possible bias
	  o Peer review
	• Background science:
	  o Hypothyroxinemia for MCLG setting
	  o Improve clarity/transparency
	  o Main source of perchlorate
	  o Other health effects
	  o Perchlorate occurrence
	  o Confounders (other goitrogens)
	• Analytical approach – connect to neurodevelopment with Epi:
	  o Uncertainties – Digitization of figures
	  o Improve clarity/transparency
	  o Confounders
	  o Inherent conservatism
	  o Presentation of conclusions
	• Analytical approach – Appendix Approach:
	  o Relevance of Steinmaus et al. analysis
	• Analytical approach – shifting hX dist:
	  o Improve clarity/transparency

Perchlorate Study Group (including comments prepared by Intertox, Inc.)	

48 pages	• BBDR model:
	  o Confounders (other goitrogens)
	  o Hypothyroxinemia for MCLG setting
	  o Improve clarity/transparency
	  o Inherent conservatism
	  o Weak TSH response
	  o Deriving the distribution of fT4
	  o Low iodine predictions
	  o Mechanism of action
	  o Model output
	• Background science:

Table 1. Summary of Technical Related Public Comments Submitted to Docket EPA-HQ-OW-2016-0438

No. of Pages	Topics covered
	○ Hypothyroxinemia for MCLG setting ○ Iodine deficiency vs. perchlorate ○ Neurodevelopmental tests ○ Other health effects • Analytical approach – connect to neurodevelopment with Epi: ○ Use of fT4 to connect to neurodevelopment ○ Confounders ○ Significance of effect ○ Uncertainties – Population evaluated • Literature Review: ○ Risk of possible bias ○ Improve clarity/transparency ○ Animal studies ○ Confounders ○ Misclassification of studies ○ fT4 measurement • Analytical approach – Appendix Approach: ○ Relevance of Steinmaus et al. analysis • Analytical approach – shifting hX dist: ○ Hypothyroxinemia for MCLG setting
The US Conference of Mayors (USCM)	
2 pages	• BBDR model: ○ Improve clarity/transparency ○ Model uncertainty • General comments: ○ Uncertainties within the model, approaches and/or studies
Western Growers	
1 page	• General comments: ○ Hypothyroxinemia

Attachment 1

Public Comments

American Chemistry Council

November 20, 2017

Mr. Samuel Hernandez
U.S. Environmental Protection Agency (EPA)
Office of Ground Water and Drinking Water
Standards and Risk Management Division
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

Submitted via the Federal eRulemaking Portal: http://www.regulations.gov

RE: Peer Review Materials To Inform the Safe Drinking Water Act Decision Making on Perchlorate, Docket No. EPA-HQ-OW-2016-0438 (82 Fed. Reg. 43354, Sept. 15, 2017)

Dear Mr. Hernandez:

The American Chemistry Council[1] (ACC) is pleased to submit these comments on EPA's proposed Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate,[2] specifically, the Draft Report: Proposed Approaches To Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water ("draft MCLG Approaches Report").[3] ACC supports the use of the best available science to support regulatory actions for perchlorate, which remains one of the most well-studied drinking water contaminants,[4] with detailed information on the health effects, mode of action (MOA), and dose-response.

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[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $768 billion enterprise and a key element of the nation's economy. It is among the largest exports in the nation, accounting for 14 percent of all U.S. goods exports. Chemistry companies are among the largest investors in research and development, investing $91 billion in 2016.
[2] 82 Fed. Reg. 43354 (Sept. 15, 2017).
[3] EPA. 2017. Volumes I, II, and III.
[4] See Cotruvo, J. 2015. Perchlorate in US Drinking Water: Is a Federal Regulation Needed to Protect Public Health? *J AWWA*, 107(6):66–71.

ACC supports and incorporates by reference the comments submitted by the Perchlorate Study Group on technical issues associated with each modeling approach presented by EPA.

Modeling Approaches

ACC continues to support EPA's commitment to derive a maximum contaminant level goal (MCLG) for perchlorate using a biologically based dose-response (BBDR) model and MOA information rather than the default MCLG ("algebraic") approach using the reference dose (RfD) with uncertainty factors and associated exposure assumptions[5]—if conducted transparently, systematically, and with appropriate consideration of peer reviewer and other submitted comments. This is consistent with EPA's Scientific Advisory Board (SAB) panel recommendation that EPA develop a physiologically-based pharmacokinetic/ pharmacodynamics (PBPK/PD) modeling approach to support the development of a National Primary Drinking Water Regulation (NPDWR) for perchlorate.[6]

It remains difficult to review and comment on the modeling approach and MCLG development process without knowing how EPA will use the revised BBDR model going forward: "EPA will present an array of approaches to inform the derivation of an MCLG for perchlorate for expert peer review."[7] This concern was emphasized by the first peer review panel in its report to EPA: "Models can always be improved, but the goal is to have a model that is fit for the intended purpose; the lack of a clear definition of that purpose for this model (i.e., how the model outputs would be used in developing the desired drinking water regulations) contributed to the difficulty the peer reviewers had in assessing whether the model was sufficiently good to apply."[8]

Further, although EPA describes two modeling approaches to support development of an MCLG in the Executive Summary of the report, in fact, three different approaches are discussed in detail in the draft MCLG Approaches Report.[9] A brief summary of all three approaches and some of their limitations are provided below.

Approach 1: The revised BBDR model is used in a "two-stage" approach to estimate maternal free thyroxine (fT4) levels with different intake levels of iodine and perchlorate. A modeled change in fT4 ("stage 1") is used to estimate neurodevelopmental deficits in offspring based on quantitative outcomes derived from five[10] epidemiological studies

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[5] ACC Comments dated Nov. 23, 2016, Docket ID No. EPA-HQ-OW-2016-0438-0009.
[6] EPA/SAB. 2013. SAB Advice of Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004.
[7] 82 Fed. Reg. at 43355.
[8] Versar, Inc. 2017. External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water, at 2.
[9] EPA. 2017. Volume I.
[10] Finken et al., 2013; Korevaar et al., 2016; Pop et al., 1999, 2003; and Vermiglio et al., 2004.

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("stage 2"), none of which are based on a U.S. population nor provide specific information on iodine intake levels. The revised BBDR model does not include other goitrogens (i.e., goiter-causing substances) with the same MOA as perchlorate,[11] despite EPA's Office of the Inspector General (OIG) recommending the use of cumulative risk assessment for perchlorate and other common dietary thyroid iodide uptake inhibitors, nitrate and thiocyanate.[12] The OIG report also noted that perchlorate accounted for less than 1% of total goitrogen load on the thyroid, and that increasing maternal total dietary intake of iodine would be the most effective approach for reducing neurodevelopmental risk to fetuses and infants.

Approach 2: The revised BBDR model is used in an "alternative population-based" approach to estimate a population shift of hypothyroxinemic pregnant women that would result from exposure to perchlorate. As discussed below, hypothyroxinemia is not considered an adverse, treatable endpoint. Also, the selection of 1 and 5% increases in the proportion of hypothyroxinemic women to define a population shift is unsupported.[13]

Approach 3 (described in "Appendix B" but not discussed in the Executive Summary): The results of a single study (Steinmus et al., 2016)[14] are used to evaluate the revised BBDR model by predicting a relationship between perchlorate exposure and maternal fT4. A change in fT4 is used to predict neurodevelopmental deficits in offspring based on epidemiological studies (only one study is used as a demonstration).

> **Recommendation – EPA should discuss the viability, including strengths and limitations, of the third approach to derive an MCLG as part of revisions to the MCLG Approaches Report—particularly in the Executive Summary.**

Iodine-Deficient Sensitive Subpopulation and Hypothyroxinemia

EPA's continued focus on a nutritionally iodine-deficient subpopulation of pregnant women as sensitive population as the basis of its BBDR modeling—and subsequent development of an NPDWR—is unprecedented.

EPA's modeling approaches continue to focus on "hypothyroxinemia"—a condition that occurs when fT4 levels are decreased while thyroid-stimulating hormone (TSH) levels are maintained in the normal range—as an indicator of potential adverse health effects resulting from exposure to perchlorate. According to the National Research Council's seminal review of perchlorate, the critical effect for perchlorate exposure is

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[11] EPA. 2017. Volume I, at 3-15.
[12] EPA/OIG. 2010. Scientific Analysis of Perchlorate. Report, 10-P-0101.
[13] EPA. 2017. Volume I, at 7-4.
[14] Steinmus et al. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. *Environ Health Perspect*, 124:861–867.

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hypothyroidism or its precursors.[15] Nevertheless, EPA's 2016 draft model report stated that hypothyroxinemia is considered a more sensitive and therefore better "indicator of the potential adverse health effects than the more pronounced decreases in thyroid function associated with hypothyroidism."[16] However, there is no clinical definition of hypothyroxinemia and it is not characterized as an adverse effect or condition by the American Thyroid Association, American Congress of Obstetricians and Gynecologists, or American Academy of Pediatrics. Nor is it typically treated as a medical condition. Rather, and as noted in ACC's 2016 comments, its MOA is unknown and could be adaptive or compensatory—neither of which is adverse. There is also no clear fT4 reference range to define the condition. To date, early pregnancy hypothyroxinemia intervention studies have not demonstrated improvements in neurodevelopmental outcomes.[17]

> **Recommendation – EPA should provide additional justification for its continued reliance on hypothyroxinemia as the critical endpoint for determining and modeling adverse effects associated with perchlorate exposure and development of a NPDWR.**
>
> **Recommendation – EPA should acknowledge the exceptionally conservative nature of the selected modeling approach, critical effect, and subpopulation. Their use should correspond with a significant reduction in or elimination of the use of uncertainty factors in the subsequent development of an MCLG, which could contribute to an overly conservative NPDWR.**

Appropriateness of Neurodevelopmental Testing

The purpose of the neurodevelopmental (global cognitive) tests used in Approach 1[18] is to identify gross deficiencies to provide specialized support and learning—not to (1) differentiate between small individual differences, (2) define and model the effect of small changes in thyroid hormones, or (3) define and model long-term deficits associated with exposure to perchlorate. Further, neurodevelopment is multifactorial and test results in children are not predictive of adult intelligence. Therefore, it is difficult to associate what level of predicted change in thryroid hormones is adverse either to the individual or the population, or to characterize the uncertainties associated with their use.

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[15] National Research Council. 2005. Health Implications of Perchlorate Ingestion. Washington, DC: National Academies Press.

[16] EPA. 2016. Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses, at 6.

[17] Funica et al. 2015. Update on a new controversy in endocrinology: isolated maternal hypothyroxinemia. *J Endocrinol Invest*, 38(2):117–123.

[18] Bayley's Scale of Infant and Toddler Development, Psychomotor Index and Motor Index (Pop et al., 1999 and 2003); Amsterdam Neuropsychological Tasks, standard deviation of reaction time (Finken et al., 2013); Snijders-Ooomen Niet-Verbale Intellegentia Test, IQ (Korevaar et al., 2016); and Wechsler Intelligence Scale for Children, IQ (Vermiglio et al., 2004).

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Peer Review
ACC commends EPA for conducting two separate peer review panels to evaluate (1) the draft BBR model and draft model report,[19] and (2) its application to develop a drinking water standard for perchlorate.[20]

> **Recommendation – EPA's peer review processes should result in consensus-driven reports by the panel rather than simply reflecting the individual perspectives of the panel members, which was largely the case in the first peer review.**

ACC appreciates consideration of these comments by EPA and the second peer review panel. Should you have questions or would like to discuss these comments, please contact me at judith_nordgren@americanchemistry.com or Mark Gibson at mark_gibson@americanchemistry.com.

Sincerely,

Judith Nordgren
Managing Director
Chlorine Chemistry Division

[19] Versar, Inc. 2017.
[20] 82 Fed. Reg. 43361 (Sept. 15, 2017).

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American Water Works Association

(including comments prepared by Ramboll Environ US Corporation and ScitoVation)

American Water Works Association

Dedicated to the World's Most Important Resource®

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November 20, 2017

SUBMITTED VIA E-MAIL

Mr. Michael H. Shapiro
Acting Assistant Administrator
USEPA, Office of Water
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

RE: Comments on the draft Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438)

Dear Mr. Shapiro:

The American Water Works Association (AWWA) appreciates the opportunity to review and comment on the Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal (MCLG) for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438).

We recognize and support EPA's efforts to address the recommendations made by the Science Advisory Board in 2013. Our review of the proposed MCLG approach and biologically based dose-response (BBDR) modeling for perchlorate has identified several areas of concern that should be considered closely by the Agency and the selected peer reviewers. A detailed assessment is attached, but in general terms the results of our review yielded the following overall conclusions:

1. The BBDR is not capable of adequately predicting iodine uptake or free thyroxine (fT4) based on attempts to simulate multiple key studies measuring perchlorate inhibition of iodine uptake, which is a necessary precursor to thyroid effects.
2. Several modeling assumptions are not appropriately documented or are based on insufficient data. This results in increased uncertainty associated with the scientific integrity of the model required to support the proposed MCLG approach.
3. EPA's process for selecting key studies linking changes in fT4 levels and neurodevelopmental effects in the proposed MCLG approach was (a) not transparent

and (b) introduced additional uncertainty, especially when confounding variables (e.g., hCG, iron deficiency) are not controlled.

In summary, while EPA's efforts to address the SAB recommendations are laudable, we believe the proposed approach contains significant uncertainties and is, therefore, insufficient for supporting a risk assessment. Until the uncertainties in the current MCLG approach can be addressed, EPA should continue to rely on the RfD recommended by the National Academy of Sciences for considering further regulatory action. The results of the modeling simulation we prepared for this review of the MCLG approach confirmed the conclusions of prior studies that low levels of perchlorate have no demonstrated health consequence that can be scientifically validated with the confidence necessary to support the proposed MCLG approach.

Should you have questions or would like to discuss this matter, please contact me (tmehan@awwa.org) or Kevin Morley (kmorley@awwa.org).

Sincerely,

G. Tracy Mehan, III
Executive Director – Government Affairs

cc: Peter Grevatt – EPA/OW/OGWDW
Eric Burneson – EPA/OW/OGWDW/SRMD
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Prepared for
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COMMENTS ON USEPA 2017:

"PROPOSED APPROACHES TO INFORM THE DERIVATION OF A MAXIMUM CONTAMINANT LEVEL GOAL FOR PERCHLORATE IN DRINKING WATER"

RAMBOLL ENVIRON

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EXECUTIVE SUMMARY

The document provides comments on the US Environmental Protection Agency's (USEPA) 2017 report entitled "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", which was prepared by the USEPA's Office of Ground Water and Drinking Water (USEPA 2017). In this report, USEPA (2017) is proposing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate in accordance with recommendations made from previous reviews conducted by the USEPA's Science Advisory Board (SAB). This MCLG approach (USEPA 2017) includes revisions to a previously developed and peer reviewed biologically-based dose-response (BBDR) model that has been extended to predict the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages. These revisions, suggested by the SAB (2013), include the following:

- Derivation of a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling;
- Expansion of the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilization of a mode of action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; and
- Extension of "the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB 2013, p. 19).

USEPA's (2017) attempts to address SAB's recommendations should be applauded. Revisions presented in the report include methods that extend the model to early pregnancy and incorporate biological feedback control of hormone production via TSH signaling, adding a description of the impact of lower levels of iodide nutrition. In addition, an attempt has been made to calibrate the model's behavior for upper and lower percentiles of the population, as well as the population median for thyroid hormone production. Finally, an uncertainty analysis for key parameters was conducted.

For the development of the MCLG, USEPA has proposed a two-stage approach linking the revised BBDR model results ("Stage 1") with quantitative information on neurodevelopmental outcomes from epidemiological studies ("Stage 2"). Stage 1 describes the thyroidal hormone levels in women of childbearing age with low to adequate iodide intake. In this stage, the revised BBDR model is applied to predict the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. Data for Stage 2 of the approach is provided from epidemiological studies evaluating maternal thyroid hormone levels in early pregnancy and the relationship between changes in these levels and the observation of neurodevelopmental outcomes. USEPA (2017) has also developed an alternative population-based approach that uses the revised BBDR model to estimate changes levels of selected thyroid hormones, specifically free T4, resulting from perchlorate exposure that may result in a shift in the population of hypothyroxinemic pregnant women.

Following a review of USEPA (2017), comments were prepared and organized around three main topics:

- USEPA model revisions including those for extending the model to early pregnancy, incorporating biological feedback control of hormone production via TSH signaling, calibrating the model and evaluating its behavior, and conducting an uncertainty analysis for key parameters. This includes comparison of model output to results from key studies, including

those identified in previous assessments, including results reported by Greer et al. (2002), Braverman et al. (2006), and Téllez Téllez et al. (2005a, 2005b);

- Linking BBDR results to neurodevelopmental outcomes focusing on the identification of published literature to develop the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes; and
- Comparison of the results from the BBDR modeling and MCLG approach with results and key studies from previous USEPA assessments.

The results of our review of the EPA's proposed MCLG approach (EPA 2017) and BBDR modeling for perchlorate yielded the following overall conclusions:

- While we applaud the EPA for the application of a BBDR model in the MCLG approach, as these models integrate the available science for a compound of interest, there is some concern that uncertainties inherit in the model call into question its proposed application in the risk assessment for perchlorate and whether it is fit for that purpose. While the hormone component of the model is a definite scientific improvement in terms of incorporating the available biology, there is a lack of data to provide validation of multiple steps in the proposed approach and of the assumptions/parameters within the biologically based dose-response (BBDR) model.
- Many of the changes in free thyroxine (fT4) that are predicted by the MCLG approach to impact the population distribution of fT4 and therefore result in per unit changes in neurodevelopmental outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to suggest that the extended version of the BBDR model has a capability to estimate small changes in fT4 with precision that is not demonstrated by any adequate validation. Further, the model predictions of fT4 underpredict observed data in various clinical studies by substantially more than 1.3-4.3%. This suggests that the model is not precise enough to predict such small changes in fT4. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as to whether these slight changes could be measured clinically, considering the greater impact of iodine intake on hormone levels.
- Until additional data are available to validate current extensions of the BBDR model to the pregnant woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake and, therefore, impacts on fT4. Based on recommendations from the National Research Council (2005), points of departure provided by these studies used in combination with uncertainty factors were considered to be protective of sensitive subpopulations, and provides a basis for future risk management decisions.

Therefore, we conclude that while the MCLG approach as proposed by USEPA incorporates additional science into the process, it still contains significant uncertainties that call into question the use of this approach to support a regulatory decision. Until the uncertainties in the current MCLG approach can be addressed, USEPA should continue to rely on the RfD recommended by the NAS for considering further regulatory action.

1. MODEL REVISIONS

1.1 Extending the Model to Early Pregnancy

The MCLG approach (USEPA 2017) is based on a hypothesized mode of action for neurodevelopmental outcomes associated with the development of hypothyroxinemia as a result of perchlorate exposure. The sensitive populations of concern for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women. Extending the model to predict the impact of perchlorate exposure on fT4 during early pregnancy is complicated by the significant variability in the levels of fT4 in the general population and the challenges in measuring fT4, as well as by the uncertainty in the identification of an alteration that may over time change fT4 from an individual's "set-point" and therefore potentially impact circulating levels in both the mother and the fetus.

According to the "American Thyroid Association Task force on Thyroid Disease During Pregnancy and Postpartum", isolated hypothyroxinemia is defined as a normal maternal TSH concentration in conjunction with fT4 concentrations in the lower 5th or 10th percentile of the reference range (Stagnaro-Green et al. 2011). USEPA (2017) has also focused on selected percentiles of the reference range; however, reference ranges can vary from population to population (Alexander et al. 2017). Even within US populations and across ethnic groups, the 2.5th percentile can vary by up to 2 pmol/L or approximately 20% (9.3-11.4 pmol/L as reported by Alexander et al. (2017)).

The variation in fT4 reported in the published literature during early pregnancy is provided in USEPA (2017), Appendix A, Figure A-33. The levels of fT4 during early pregnancy, based on the studies identified by USEPA (2017), appear to range from approximately 12-16 pmol/L. This range is consistent with the range of fT4 means reported in the Greer et al. (2002) study at baseline of approximately 1.2 ng/dL (15.5 pmol/L). However, the 50th percentile model predictions at zero dose perchlorate and 170 µg/day iodine intake (approximately 10 pmol/L at gestation weeks 12, 13, and 16) are much lower than these reported values.

Measuring fT4 in the presence of high concentrations of bound T4 is challenging, especially in conditions where binding proteins are altered such as during pregnancy (Alexander et al. 2017). Measurement techniques are prone to inaccuracy during pregnancy due to disruption of the original equilibrium. The 95% fT4 reference intervals decrease gradually with advancing gestational age: from 1.08– 1.82 ng/dL (approximately 13.9 – 23.5 pmol/L) in week 14 to 0.86–1.53 ng/dL (approximately 11.1 – 19.8 pmol/L) in week 20.

In addition, as noted in USEPA (2017):

> *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see Figure 2) that operates around a "set-point." This set-point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance (Andersen, Pedersen, Bruun, & Laurberg, 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations (Andersen et al. 2002)."*

Extending the thyroid BBDR model to address early gestation is a significant challenge due to the complex interaction between thyroid homeostasis and gestational development. While the model appears to accurately simulate average fT4 in early gestation in the absence of perchlorate exposure, (Figure A57 in Appendix A), a previous peer review panel noted that

the model of early 2017 was most appropriate for higher iodide and lower or zero perchlorate exposures. Considering the addition of TSH feedback dynamics, and an adjustment factor to match specific population percentiles, there is reason for concern regarding the uncertainty of the revised model predictions under low iodide intake conditions. Some of these concerns are highlighted below:

- In addition to regulation by TSH, hCG levels rise in early pregnancy and this increases NIS uptake activity and T4 production. hCG is structurally similar to TSH, and stimulates iodide transport and thyroid hormone synthesis through stimulation of the TSHR. In the model, the Vmax for NIS-mediated uptake is increased during pregnancy based on independent data, but that change is not described as a function of hCG. "VmaxNISF_thy_I is scaled to increase with pregnancy based on an empirical relationship between gestational age and radioactive iodide uptake." hCG is calculated as a function of gestational age, and is then used to increase T3 and T4 production, but the increase in thyroidal iodine uptake is mistakenly ascribed by the model to TSH. This suggests that the model structure is not true to the biology, introducing uncertainty to predictions of T4 during pregnancy.
- The current model uses a baseline first-order constant calibrated to NHANES 2007-2012 median, 10th, or 90th percentile non-pregnant data. The KProdT4F value for the median NHANES calibration is 6.25*10-7 /hr/kg$^{0.75}$ (Table A-2), which is lower than 2.45 x 10-6 used by Lumen et al. (2013) based on fitting to data of Nicoloff et al. (1972). This value is scaled in pregnancy with increasing KProdT4 through GW 16 (peak occurring ~ GW 9) based upon placental hCG increase over this time according to the linear relationship from Glinoer (1997): hCGreg = 1 + 0.00354 x hCG. However, the use of a T4 production rate that is lower than the published value is not adequately justified, given the importance of this parameter, which has a direct impact on predictions of fT4 changes, for the intended application of the model.
- The current model uses a Km for perchlorate binding to the NIS (KmNIS_P) that is 3-fold lower than Lumen et al. (2013) (i.e. a 3-fold higher affinity). Specifically, Km is the 2.5th percentile lower confidence limit of the population median based upon USEPA reanalysis of Greer et al. (2002). The value (50th percentile = 0.73 μM) is similar to that obtained from re-analysis of in vitro binding data, 0.59 μM (Schlosser 2016); use of KmNIS_P = 0.489 μM makes perchlorate 3 times more effective at competitive inhibition of NIS versus Lumen et al. (2013).
- Plots of NHANES 2007-2012 data for non-pregnant women demonstrated little relationship between iodine intake and fT4, even at iodide intake levels below 75 μg/day (Figure A-54). Given limited data in this range, USEPA has used the relationship between thyroidal iodide stores (mg) and iodine intake, which shows depletion of fT4 at iodide intake levels below 100 μg/day (Delange, 2000). It is clear from Figure A-54, this is inconsistent with the NHANES data. This relationship was used as part of a parameter calibration procedure to simulate population percentiles of fT4, T4, T3, and TSH identified from NHANES data (see Appendix A, Figures 54-56)." However, script files included with the BBDR model use an iodine intake of 90 μg/day. The model is much more sensitive to iodine intake than perchlorate dose, with minimal changes to hormone levels due to perchlorate exposure at high iodine intake levels. The various iodine intake levels used for model simulations need to be more clearly presented and justified.

1.2 Calibrating the Model and Evaluating its Behavior

In development of these comments, multiple studies were independently simulated to an attempt to duplicate datasets that were reported by USEPA (2017) to calibrate the model. This included studies

to evaluate the model's behavior and determine if the results were consistent with the final values reported in the draft MCLG approach. This included:

- Comparison to the Steinmaus et al. 2016 results
- Other key studies noted in previous assessments:
  - Greer et al. 2002 – 14 day worker study
  - Braverman et al. 2006 – 6 month study
  - Téllez Téllez et al. 2005a, 2005b – Chile study (see attached)

In efforts to produce these simulations, it was noted that instructions for running the model for different scenarios, and documentation of the rationale for the model parameter values associated with them, are inadequate and lack transparency; this deficiency is exacerbated by the number of permutations of parameter settings used to generate the figures in the document. As a result it is difficult to have confidence in the results of a model evaluation, even by an experienced modeler, due to the significant uncertainties regarding the steps necessary to reproduce the figures and tables in the report, or to perform comparisons of model predictions to data for alternative exposure scenarios or studies.

1.2.1 Comparison to the Steinmaus et al. 2016 Results

In Appendix B of USEPA (2017), a comparison of the predicted changes in both fT4 and TSH from the BBDR model were compared to the results reported by Steinmaus et al. (2016). The Steinmaus et al. (2016) study was conducted to evaluate the potential for perchlorate exposure to impact thyroid hormone levels in pregnant women in San Diego. They reported an effect of perchlorate on fT4 levels to be similar among women with both low iodine (<100 µg/day) and normal (100-300 µg/day), with a greater effect of perchlorate observed among pregnant women in the high iodine intake group (>300 µg/day). They noted that this effect has been observed in NHANES evaluations

The comparison of the predicted fT4 changes from the BBDR model and the Steinmaus et al. (2016) results associated with changes in perchlorate dose are reported in Figure B-1. Duplication of this BBDR modeling output was possible using the USEPA provided modeling code, with additional instruction from USEPA staff. However, this comparison clearly highlights the differences between the model predictions and those from a published study. The baseline simulations with normal iodine intake (170 µg/day) demonstrate no change in fT4, which is consistent with other studies in which no impact on fT4 has been observed at doses up to 7 µg/kg/day (Greer et al. 2002; Braverman et al. 2006). The model underpredicts the changes in fT4, even in the scenario with low dietary iodine intake (75 µg/day), in comparison to the changes reported by Steinmaus et al. (2016). This discrepancy demonstrates the significant uncertainty in the ability of the model to predict changes in fT4 associated with perchlorate exposure. In particular, the current MCLG approach results in small changes in fT4 as low as approximately 1% being predicted to result in unit changes in neurodevelopmental endpoints. Predictions of this precision would require a level of model precision that has not been demonstrated by comparison to existing data.

1.2.2 Other Key Studies Noted in Previous Assessments:

Greer et al. 2002 – 14 day study

The Greer et al. (2002) study was conducted to establish the dose-response in humans for perchlorate inhibition of thyroidal iodide uptake and any short-term effects on thyroid hormones following exposure for male and female volunteers to perchlorate in drinking water at doses of 7, 20, 100 or 500 µg/kg/day for 14 days. The results of this study have previously been relied upon by the USEPA (2005) to derive a reference dose (RfD) and to determine health reference levels (HRLs). The results of this study indicate a decrease in iodide uptake following exposure to a dose of 20

µg/kg/day, but no effect on hormone levels, including fT4 and TSH, at the highest dose tested. A No Observed Effect Level of 7 µg/kg/day was determined based on these results, and an RfD of 0.7 µg/kg/day was adopted, based on NRC recommendations, with the application of an uncertainty factor of 10 for intraspecies variability or sensitive subpopulations.

Consistent with the results of the study, simulating the exposure of the Greer et al. (2002) with the BBDR model indicated no significant change in fT4 at doses up to 500 µg/kg/day. However, predicted concentrations of fT4 are lower than those measured by Greer et al. 2002. The model simulation was run with an iodine intake of 90 µg/day, as this was the value USEPA used in the Greer_test.m script. However, 90 µg/day is not consistent with the 170 µg/day value EPA reports as representing a sufficient intake and USEPA's documentation does not indicate why a lower value was used for the individuals in the Greer study. Simulation of iodide uptake inhibition (RAIU) appears to over-predict the measured values, though the qualitative increasing trend of inhibition with dose behaves appropriately. This discrepancy may result from the low iodine intake chosen by USEPA.

Table 1. Simulation of the Greer et al. (2002) Perchlorate Study

Dose	RAIU (%)		fT4 (pM)	
(ug/kg/d)	Simulated	Measured	Simulated	Measured
0	100	100	10.33	-
7	89	98.2	10.33	-
20	74	83.6	10.32	16.09
100	37	55.3	10.31	15.26
500	11	32.9	10.30	15.44

Braverman et al. 2006 – 6 month study

The Braverman et al. (2006) study was conducted to determine whether prolonged exposure (6 months) to low levels of perchlorate (0.5, 1.0 or 3.0 mg/day) would perturb thyroid function. The study included a small number of individuals; however, iodine levels were comparable with those of the general population. The authors noted the limitations of the small sample size, but concluded that the results suggested that healthy, euthyroid individuals, with normal levels of iodine intake, can tolerate chronic exposure to perchlorate at doses of up to 3 mg/day (approximately 40 µg/kg/day) without any effects on thyroid function, including inhibition of iodine uptake.

The Braverman et al. study was simulated using the BBDR model, and predicted T3 and TSH levels were compared to the reported measurements. fT4 was not compared because it was not clear how to convert the T4 index to a concentration and vice versa. As with the Greer simulation, 90 ug/day was used for iodine intake. Baseline T3 and TSH are similar to the measured values. But, as was seen with fT4, the simulated change in hormone levels is severely dampened compared to the measured values.

Table 2. Simulation of Braverman et al. (2006) perchlorate study.

Dose	T3 (nM)		TSH (mIU/L)	
(ug/kg/d)	Simulated	Measured	Simulated	Measured
0	2.63	2.49	1.51	1.20
7	2.63	2.51	1.52	1.60
43	2.62	1.77	1.53	2.60

Téllez Téllez et al. 2005a, 2005b – Chile study in pregnant women

Téllez Téllez et al. (2005a, 2005b) reports the results of a longitudinal epidemiological study among pregnant women from three cities in Chile exposed to concentrations of perchlorate as high as 114

µg/L in the public drinking water. The focus of the study was to evaluate maternal thyroid function during pregnancy, neonatal thyroid function and developmental status at birth, and breast milk iodine and perchlorate levels during lactation. The National Academy of Sciences (2005) has reviewed this study in the context of health implications for perchlorate ingestion and concluded this study should be considered in the evaluation of the U.S. experience with perchlorate in drinking water. The total iodine nutrition among this cohort was also noted to be similar to that of U.S. pregnant women (Téllez Téllez et al. 2005a); therefore, this study should be a key consideration in evaluating the relationship between perchlorate exposure, changes in fT4 in pregnant women and developmental status.

Results from this study, relied upon for BBDR model parameters (specifically the elimination to urine parameter – CLFUP), indicated no effect on thyroid levels in early pregnancy, late pregnancy, or neonates at birth related to perchlorate in drinking water at concentrations up to 114 µg/L. It seems this study should provide a validation dataset for the impact of high concentrations of perchlorate exposure in drinking water on potential changes in fT4 or TSH.

The BBDR model was used to simulate the drinking water study. The predictions of fT4 are consistent with the negative results of the study, though the concentrations are again smaller than those observed. This is not a strong validation of the model given the weak trend of changes in hormone levels seen in comparisons to other studies.

Table 3. Simulation of the Tellez et al. study of pregnant women exposed to perchlorate via drinking water.

Dose	fT4 (pM)	
(ug/kg/d)	Simulated	Measured
0.01	9.74	12.5
0.08	9.73	12.2
2	9.69	12.7

Overall, the BBDR model reproduces the key elements of the findings from these three studies, which indicate that thyroid hormone levels are relatively insensitive to inhibition of thyroid iodine uptake by perchlorate concentrations several orders of magnitude higher than those predicted by the BBDR to affect fT4 in early pregnancy. In particular, it seems biologically implausible that concentrations of perchlorate up to 2 ug/kg/d were demonstrated to be without effect to pregnant women in the Tellez study, while the BBDR model predicts that perchlorate concentrations nearly an order of magnitude lower could result in changes in fT4 during the first trimester. During the first trimester, hCG increases the iodine uptake capacity of the thyroid and the T4 production rate so significantly that TSH concentrations are typically reduced. The BBDR model assumes that during the first trimester thyroid hormone production is controlled by both TSH and hCG but thyroid uptake is controlled by TSH only. However, hCG controls both organification and uptake. During pregnancy, hCG stimulates iodide transport and thyroid hormone synthesis through stimulation of the TSH receptor due to the structural similarity of hCG to TSH. This increase typically results in lower TSH levels (Pesce and Kopp 2014). Thus, during the first trimester, the thyroid is actually in a better position to respond to inhibition of iodine uptake through a direct TSH-mediated response if needed.

2. LINKING BBDR RESULTS TO NEURODEVELOPMENT OUTCOMES

Chapter 5 of USEPA (2017) focuses on the SAB's recommendation to "Identify literature and conduct analyses to support the model outputs for the downstream steps" from the BBDR's predicted changes in thyroid hormones following exposure to perchlorate. Specifically, Chapter 5 was developed to present the process USEPA used to identify literature to support the approach for derivation of the MCLG for perchlorate. USEPA (2017) states, "Based on the recommendations of previous peer review panels, USEPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes", and because of this assumption, a complete systematic review of the body of literature on this topic was not performed. Instead, a "focused review of the published literature" was conducted.

The approach is inconsistent with recent recommendations from the National Research Council regarding systematic review and evidence integration (NRC 2014). These recommendations are currently being incorporated into the USEPA's Integrated Risk Information System (IRIS) process and USEPA has recently released scoping and problem formulation materials for several new Integrated Risk Information System (IRIS) assessments, including ethylbenzene (USEPA 2014a), and naphthalene (USEPA 2014b). The approach applied in these assessments is intended to follow recommendations provided by the National Research Council (NRC 2013). While development of MCLGs are not part of the IRIS process, the application of systematic review principles in the identification of studies to define the relationship between fT4 and neurodevelopmental effects, is needed. The application of these principles will not only assist in defining the highest quality studies to address a specific research question, they provide a way to integrate all of the available evidence for the specific research questions raised by the SAB. Systematic reviews include the formulation of a specific question to be addressed and developing a protocol that specifies the methods that will be used to address the question. While a broad research question can lead to a large systematic review, if the research question is limited, such as in the case of perchlorate, then the systematic review becomes more focused.

For the USEPA (2017) MCLG approach, a systematic review question could have been easily developed based on the SAB recommendation (i.e. "Identify literature and conduct analyses to support the model outputs for the downstream steps") and the protocol would simply be focused on the methods for conducting the systematic review to address this very focused systematic review question in a transparent manner. Transparency being defined by USEPA as "sufficient information will be available to understand the scientific rational behind decisions, as well as, reproduce methods used to identify and evaluate data". However, in the case of the literature identified for consideration in the MCLG approach for perchlorate, a well-defined protocol for all steps of the process has not been developed and therefore is inconsistent with the recommendations of the NRC (2013):

> *"A priori decisions and a predefined protocol are critical during the systematic review process (Berlin and Colditz 1999; Dickersin 2002); the protocol should describe the following steps: the research question, the search strategy and data sources, the study inclusion and exclusion criteria, the data to be abstracted and derived from the original studies (such as sample size, exposure and outcome assessment methods, and confounders evaluated), the criteria and methods for pooling effect estimates and measures of variability among studies. Systematic reviews and meta-analyses need to be replicable; other investigators following the same steps should be able to identify the same articles, abstract the same data, and reach similar conclusions."*

At each step of the process for identifying studies for use in the development of the MCLG approach for perchlorate, a detailed set of criteria is needed. For example, if decisions are made to include or exclude any studies, there should be very detailed criteria indicating why studies were included or excluded and it should be specified prior to the initiation of the literature searching process. The criteria for each step should be described in such a way that an independent reviewer could use it to replicate the results of the literature search and review; however, there are several areas in the USEPA (2017) MCLG approach for perchlorate where this level of detail is lacking, making it difficult for an independent reviewer to replicate the results.

2.1 Systematic Review Research Questions

An overall hypothesis or systematic review research question should be developed that is based on the SAB recommendation to clarify the focus of the review and the linkage between altered maternal fT4 (as predicted by the BBDR model) and the potential for adverse neurodevelopmental effects in offspring. Some additional explanation as to how USEPA arrived at the specific neurodevelopmental outcomes of concern should be provided.

2.2 Searching the Published Literature

While the literature search key words are presented in the USEPA (2017) report, there is a lack of explanation as to the reasoning behind the focus on the outcome of concern. The research question should be used to develop the literature search. The major points used or considered in developing the literature search strategy should be presented. In addition, there should be a detailed explanation of the screening criteria used to screen the literature search results. Furthermore, USEPA (2017) does not report the details of the literature search results. For each search string reported in Table 9 of the USEPA (2017) report, a total number of citations identified should be reported. In addition, the criteria used to screen the original search results should be clearly reported in the document. Essentially, each step of the literature search and review should be reported in such a way that any independent party could easily reproduce the results reported in Chapter 5 of USEPA (2017). The lack of this type of information does not allow the reader to determine if any key studies may have been removed from consideration.

2.3 Literature Screening Approach and Selection of Key Studies

USEPA (2017) states that a 3 step approach was used to identify studies for consideration in the development of the approach for derivation of the MCLG for perchlorate. The approaches utilized by USEPA (2017) to identify the epidemiological studies for this evaluation were strictly focused on the appropriateness of the quantitative data for consideration in combination with the output of the BBDR model. Group 2 (studies with categorical analyses only) and Group 3 (studies with analyses not directly compatible with BBDR output) studies were apparently eliminated from consideration in the assessment. While not directly compatible with BBDR modeling output, it is possible that these studies may provide information important in understanding the potential relationship between changes in thyroid hormones and the potential for neurodevelopmental effects, as well as potential key confounders.

While 15 studies were identified in Group 1, only 5 of these were determined by USEPA to include analyses that could be used to connect the results of the BBDR model to incremental changes in adverse neurodevelopmental effects. A clearly defined set of inclusion and exclusion criteria should be developed to clearly convey to the reader why the other 40 studies in Groups 1, 2, and 3 were not considered. In addition, studies that provide no evidence of an inverse relationship between perchlorate exposure and serum thyroid function (e.g. Ghassabian et al. 2014; Modesto et al. 2015; Moleti et al. 2016; Noten et al. 2015) should also be considered to not only understand why these

results are in contrast to the potential research question, but also that the overall weight of evidence can be determined. It is possible that the majority of studies provide evidence that critical factors that are not reported in some of the available studies may explain the reported changes in serum thyroid function.

2.4 Assessment of Study Quality and Risk of Bias

According to recent recommendations from the National Research Council (NRC 2014), the National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT) method for the assessment of study quality and risk of bias of the literature (NTP 2015) is one method that should be considered for qualitative and quantitative assessments. "An assessment of study quality evaluates the extent to which the researchers conducted their research to the highest possible standards and how a study is reported. Risk of bias is related to the internal validity of a study and reflects study-design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect" (NRC 2014). Each study meeting inclusion criteria in Group 1, 2, and 3, should be evaluated against a predetermined set of study quality and risk of bias criteria and the results of this evaluation should be presented in the perchlorate MCLG approach report.

2.5 Uncertainties Critical to Characterizing Changes in Thyroid Hormone Levels in Pregnant Women Associated with Neurodevelopmental Changes in Offspring

The MCLG approach presented in USEPA (2017) to predict doses of perchlorate that would result in per unit changes in neurodevelopmental measures, is, as noted by USEPA (2017), "…dependent upon predictions from the BBDR model, the derivation of the distribution of fT4, and the evaluations of the relationship between fT4 and neurodevelopment. Each of these steps has inherent uncertainties associated with it."

A major source of uncertainty is related to the five studies in Group 1 with data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment (Pop et al. 1999, 2003; Finken et al. 2013; Korevaar et al. 2016; Vermiglio et al. 2004). None of these five studies relied upon data from US populations or have been demonstrated to have iodine intake similar to US populations. Yet according to Alexander et al. (2017) the reference range of both TSH and fT4 in pregnant women varies depending upon ethnicity. While two studies in Group 1 focused on population groups within the United States, neither were considered for the model because T4 and not fT4 was measured in the pregnant females (Oken et al. 2009) and the relationship between fT4 and neurodevelopment was evaluated in late pregnancy and did not reach statistical significance (Chevrier et al. 2011). USEPA (2017) (Section 6.5.1) states "there is no reason to believe that the impact of fT4 on neurodevelopment would differ by country, unless there is a substantial difference in iodine intake". While USEPA (2017) does make an effort to evaluate changes in iodine intake in women from various populations, including the US, there are not substantial data reported to validate the conclusions that the impact of fT4 on neurodevelopment would differ by population or uncertainty in iodine intake levels would have an impact on the derivation of the MCLG. This is inconsistent with data from the American Thyroid Association (Alexander et al. 2017) that suggest variability in the distribution of thyroid hormone levels across populations and even within ethnicities within a single population.

USEPA (2017) also notes that all five studies used for quantitative analysis relied on a one-time fT4 level during pregnancy (Section 6.5.5). The influence of changes in maternal fT4 on fetal brain development is likely greatest during early pregnancy. The variability in maternal fT4 levels during pregnancy and the lack of measurement of fT4 at time points throughout pregnancy in the studies relied upon introduces a significant amount of uncertainty to the assessment. As stated in USEPA (2017),

> *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see Figure 2) that operates around a "set-point." This set-point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance (Andersen, Pedersen, Bruun, & Laurberg, 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations (Andersen et al., 2002)."*

Several other areas of uncertainty are also highlighted by USEPA (2017). Specifically, USEPA (2017) noted that none of the five studies carried forward provided iodine intake levels (Section 6.5.3), which adds significant uncertainty to the estimates. Three of the 5 studies (Pop et al. 1999, 2003; Vermiglio et al. 2004) also have populations of less than 30 decreasing the statistical power of the studies (section 6.5.4) relied upon for establishing the relationship between changes in fT4 and neurodevelopmental changes. USEPA (2017) also noted uncertainties in regards to the analytical methods used to evaluate fT4 levels and while approaches are being introduced to standardize analytical methods, results at different time points and from different countries may vary considerably due to differences in analytical procedures (USEPA 2017). USEPA (2017) also notes that "there is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. This is exemplified by the fact that in this analysis larger unit changes are being seen with increasing percentiles of fT4 in most analyses." Finally, other confounders such as iron deficiency were not considered in the analysis. Iron deficiency in pregnant mothers may also be associated with hypothyroxinemia (Yu et al., 2015) and failing to directly account for a relationship between iron deficiency and hypothyroxinemia may introduce an uncertainty into this analysis.

While all of these uncertainties are noted by USEPA (2017), there is no attempt to adjust the MCLG approach in any way to account for these uncertainties. Many of these, especially confounders such as iron deficiency in the study population and a lack of information on iodide intake, can have a significant effect in characterizing changes in thyroid hormone levels associated with changes in neurodevelopmental outcomes. In the absence of adequately accounting for these uncertainties, it is difficult to conclude that small changes in a specific thyroid hormone (e.g. fT4) may accurately predict the potential for neurodevelopmental effects.

3. COMPARISON TO PREVIOUS ASSESSMENTS

In the MCLG approach, USEPA (2017) has focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time) based on the measurement of fT4 during early pregnancy. Results from previous studies have provided the basis for No Observed Effect Levels (NOELs) for health effects of perchlorate in the development of Reference Doses and currently recommended Health Reference Levels (HRLs), including Greer et al. (2002) which reported results similar to the BBDR model in human test subjects. Results reported by Greer et al. (2002) in which subjects were exposed to perchlorate in drinking water at doses of 0.007, 0.02, 0.1, or 0.5 mg/kg/day for 14 days demonstrated a NOEL for perchlorate inhibition of radioiodide uptake by the thyroid NIS following exposure to 7 µg/kg/day. The point of departure from the Greer et al. (2002) study represents a perchlorate level that precedes the inhibition of iodine uptake by the thyroid. The NAS RfD developed based on the point of departure (POD) from this study is a departure from the Agency's traditional approach of using a No Observed Adverse Effect Level (NOAEL) for regulatory actions. The NAS's use of a No Observed Effect Level (NOEL) is based on "using a nonadverse effect that is upstream of the adverse effect [which] is a more conservative and health protective approach".

While these studies have not been conducted in pregnant women (the population of interest for the MCLG approach), as noted by in USEPA (2017):

> *"…the BBDR model predicts very little difference in non-pregnant and first-trimester response to perchlorate. This likely occurs because the half-life of (organified) iodine in the adult thyroid is around six months, hence the availability of thyroidal iodine in the first trimester pregnant woman is determined to a very large extent by her nutrition and perchlorate exposure several years preceding pregnancy."*

This suggests comparison of the current modeling results to those from studies conducted in adults should provide insight into the predictions of the model and the conclusions regarding the changes in thyroid hormone levels that may result in neurodevelopmental effects.

The current approach for deriving the MCLG assumes any exposure to perchlorate reduces fT4 to some extent (p. 3-17 of USEPA doc). In addition, linear regression analyses conducted to evaluate the relationship between changes in fT4 and neurodevelopmental effects further assumes any change in fT4 results in some risk of neurodevelopmental effects. These assumptions are in contrast to the results from the Greer et al. (2002) in which exposures to perchlorate were as high as 500 µg/kg/day and no impact on thyroid hormone levels was observed. This was true for both men and women. In addition, in a study conducted by Braverman et al. (2006), 6 months of exposure to perchlorate in capsules at doses up to 3 mg/day (approximately 40 µg/kg/day) was reported to have no effect on thyroid function, including inhibition of thyroid iodide uptake as well as serum levels of thyroid hormones, TSH, and Tg in a small group of volunteers.

USEPA (2017) notes (p. 6-16) that from results of the literature review, it appears the relationship between maternal fT4 and fetal brain development has a temporal relationship, with this influence likely being greatest in early pregnancy (i.e. prior to mid-gestation). The focus of the evaluation is on gestational weeks 12, 13, and 16, where the mother's fT4 levels will have the greatest impact on the fetus. This should allow for comparison to the model results in pregnant women to results from previous studies focused on identification of perchlorate concentrations that would impact fT4 levels in adult women, such as the Greer et al. (2002) study.

In comparing the current BBDR model predictions to previous assessments, in Tables 35 and 40 of USEPA (2017) a perchlorate dose of 0.3-0.4 µg/kg/day would result in a 1% increase in the

proportion of the population with hypothyroxinemia and a perchlorate dose of 2.1-2.2 µg/kg/day would result in a 5% increase in proportion of the population with hypothyroxinemia. These modeling results suggest a potential for a significant change in thyroid hormones, as well as adverse effects on neurodevelopment at doses of perchlorate exposure for which there is evidence that decreases in fT4 are not observed. Based on the mode of action proposed by USEPA (2017), decreases in fT4 and increases in TSH would be prerequisite steps for the potential for neurodevelopmental effects. These changes in hormone levels are not observed in workers in the Greer et al. study following exposure up to 500 µg/kg/day. The current assessment suggests population changes in fT4 would be observed that would shift the proportion of pregnant women that would be hypothyroxinemic at doses of perchlorate below the previously defined NOEL (7 µg/kg/day).

Table 39 of USEPA (2017) provides the predicted dose of perchlorate per unit change in neurodevelopmental measure for low iodine intake individuals. Considering multiple neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time), those for IQ are approximately at or above (6.5 – 45 µg/kg/day) the NOEL from Greer et al. (2002) and are associated with decreases in fT4 of 4.3 to 18.7%. The remaining doses associated with the other neurodevelopmental endpoints are 1.7 to 3.0 µg/kg/day and associated with decreases in fT4 of 1.3 to 2.4%. These percent changes in fT4 are very small and considering the potential uncertainty and variability in measuring fT4 levels, may not be detectable in the clinical setting. The dose of perchlorate estimated to result in a 1% or 5% increase in the proportion of hypothyroxinemic pregnant women is even lower, ranging from 0.3 to 2.2 µg/kg/day. Multiple studies in adults and pregnant women (Greer et al. 2002; Braverman et al. 2006; Téllez Téllez et al. 2005) provide evidence that no impact on iodine uptake or thyroid hormone levels would be expected at these dose levels. Based on the mode of action proposed by USEPA (2017), these events would be precursors necessary for the development of neurodevelopmental effects.

4. OVERALL CONCLUSIONS/COMMENTS

- While we applaud the EPA for the application of a BBDR model in the MCLG approach, as these models integrate the available science for a compound of interest, there is some concern that uncertainties inherent in the model call into question its proposed application in the risk assessment for perchlorate and whether it is fit for that purpose. While the hormone component of the model is a definite scientific improvement in terms of incorporating the available biology, there is a lack of data to provide validation of multiple steps in the proposed approach and of the assumptions/parameters within the BBDR model.
- Many of the changes in fT4 that are predicted by the MCLG approach to impact the population distribution of fT4 and therefore result in per unit changes in neurodevelopmental outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to suggest that the extended version of the BBDR model has a capability to estimate small changes in fT4 with precision that is not demonstrated by any adequate validation. Further, the model predictions of fT4 underpredict observed data in various clinical studies by substantially more than 1.3-4.3%. This suggests that the model is not precise enough to predict such small changes in fT4. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as to whether these slight changes could be measured clinically, considering the greater impact of iodine intake on hormone levels.
- Until additional data are available to validate current extensions of the BBDR model to the pregnant woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake and, therefore, impacts on fT4. Based on recommendations from the National Research Council (2005), points of departure provided by these studies used in combination with uncertainty factors were considered to be protective of sensitive subpopulations, and provides a basis for future risk management decisions.

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November 20, 2017

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Washington, DC 20460

Re: Docket ID No. EPA-HQ-OW-2016-0438, Request for Public Comments To Be Sent to EPA on Peer Review Materials To Inform the Safe Drinking Water Act Decision Making on Perchlorate

Dear Mr. Hernandez:

The Association of Metropolitan Agencies (AMWA) is an organization representing the largest publically owned drinking water utilities in the United States. Any changes in the development of national primary drinking water regulations significantly impact our members. EPA has published a request for comment on the draft report: *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water.* AMWA has been involved with the issue of perchlorate since EPA first began pursuing a regulatory determination.

AMWA appreciates the work that EPA has done in order to make a scientifically sound decision on the regulation of perchlorate. The multiple reviews and drafts that EPA has compiled in order to develop a reliable and precise model for determining the impact of perchlorate is a valuable scientific approach. While AMWA agrees that there is a possible correlation between perchlorate exposure and iodine uptake, which in turn may impact thyroid hormone levels, the association has concerns with the methodology of the model and its use to extrapolate possible neurological outcomes in children. AMWA is not certain that the model is precise and reliable enough to determine a thyroid hormone level that corresponds/correlates with perchlorate exposure and is concerned with the possible biases that are introduced by using the model's output with already existing neurodevelopment data from the literature in order to make conclusions on the impact of perchlorate on neurodevelopment. Due to the reasons stated above, AMWA is concerned that the methods shown in this report set a worrying precedent for regulatory determination decisions to

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CHIEF EXECUTIVE OFFICER
Diane VanDe Hei

follow.

Due to the importance of this report as it relates to the development of a maximum contaminant level goal for perchlorate, AMWA is pleased to submit these comments for the Safe Drinking Water Act decision making on perchlorate. Our specific comments are provided as an attachment. If you have any questions, please contact Stephanie Hayes Schlea (schlea@amwa.net), AMWA's Manager of Regulatory and Scientific Affairs.

Sincerely,

Diane VanDe Hei
Chief Executive Officer

Attachment

CC: Eric Burneson; Michael Shapiro

AMWA's Comments to EPA on Peer Review Materials To Inform the Safe Drinking Water Act Decision Making on Perchlorate

General Comments

1. The peer review panel in January 2017 advised EPA to include first trimester, but not to exclude the other life stages. EPA focused on only the first trimester for their revised model due to the lack of data for other stages and the stronger relationship between hormone levels and neurodevelopmental outcomes in early pregnancy. However, the original model encompassed late trimester and infancy, particularly in regards to bottle and breast-feeding infants. EPA states that excluding these stages allows for a simplified model. AMWA requests that EPA give more explanation as to why the model was limited to the first trimester instead of just expanding the original model in order to evaluate all stages. AMWA also suggests that EPA discuss the biases and uncertainties that are added to EPA's analysis by only looking at this life stage.
2. Although this has been stated in previous discussions, AMWA reiterates that a lack of iodine may be the larger factor contributing to thyroid dysfunction regardless of perchlorate exposure. According to the report, one six month study found no changes to thyroid function, but the subjects had higher than average concentrations of iodine, which the report suggests may have been protective. AMWA recommends EPA discuss the possibilities for why no change in thyroid function was found and if iodine deficiency may be the larger factor in thyroid dysfunction.
3. A second statement in the report (p. 3-13) mentions that "there is little predicted change in the percentage drop in fT4 or percentage increase in TSH between gestational weeks due to perchlorate exposure, although baseline TSH and total T4 levels do vary significantly with gestation. However, there is a significant drop in fT4 and increase in TSH with decreased iodide intake in the absence of perchlorate exposure. AMWA recommends that EPA discuss possibilities for why there is little change in fT4 due to perchlorate exposure and if the major factor again might be iodine intake.
4. According to Huber et al. (2011), drinking water contributes 20% to perchlorate intake and food contributes 80%. For the studies cited, is food intake accounted for and if so, how much effect from perchlorate is due to solely drinking water?
5. In section 8, the report lists many other possible health concerns regarding perchlorate. In particular, in section 8.3 (p. 8-2) it is stated that the Comparative Toxicogenomics Database (CTD) "identified 455 diseases potentially associated with perchlorate." However, in the paragraph below (p. 8-3) this statement it is said "connecting perchlorate with other adverse outcomes such as neurodegenerative diseases is highly uncertain at this time. Until more detailed information is collected that will allow the CTD to be used for hazard assessments, it is currently limited to hypothesizing adverse outcome pathways and designing additional studies to more completely understand the range of

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adverse health effects associated with perchlorate." What is the reasoning for including these statements linking perchlorate to a variety of conditions if it is limited to only hypothesizing?

6. There seems to be a variety of studies that conclude perchlorate does affect TSH and fT4 levels, particularly the studies used in this report, but there are also many studies that have found no correlation. For example, Pearce et al. (2010, p. 3321) found that there was "no association between urinary perchlorate levels and first-trimester serum TSH or FT_4 levels." A second study by Brent (2014, p. 4066) stated, "Perchlorate was detected in the urine of all women studied, but there was no correlation of perchlorate levels in the urine with maternal thyroid function. This finding was especially significant because the median iodine intake in Cardiff and Turin, 98 and 52 μg/L, respectively, was relatively low. Individuals with lower iodine intake are thought to be more susceptible to the negative effects of perchlorate exposure." In one of the more recent perchlorate studies (Leung, Pearce and Braverman 2014, p. 376), the conclusion was as follows; "Available data thus far have been inconsistent in demonstrating a correlation between low-level perchlorate exposure and thyroid dysfunction, particularly among those most vulnerable to even mild thyroid dysfunction. Ongoing research is needed to help better understand the potentially adverse effects of human perchlorate exposure, especially in light of recent discussion to proceed with costly longterm perchlorate regulation in U.S. drinking water."

   What reasoning does EPA have for the variation in findings from these studies? AMWA recommends that EPA discuss if there is sufficient data to determine a relationship between perchlorate and hormone levels during pregnancy, particularly at lower levels within sensitive populations.

Precision and Reliability of the Model

1. In section 3.5, it is stated that the incorporation of a feedback loop in the model introduces uncertainties. Fitzgerald and Bean (2016) are cited within the report stating that increasing TSH levels do not have a consistently predictable impact on T4 levels. The report goes on to cite Hadlow et al (2013), which indicates the relationship between TSH and T4 levels is consistently a decreasing function but that it is variable with many factors. AMWA recommends that EPA discuss how the uncertainty of this relationship impacts the reliability and precision on the model.

2. A significant portion of this report relies on the correlation between low thyroid hormone in the first trimester of pregnancy and decreased neurodevelopment. There are recent studies that have shown a high concentration of thyroid hormone may have similar detrimental effects on neurodevelopment, including one of the five case studies used for this report, Korevaar et al. (2016). AMWA recommends that EPA discuss how certain and reliable the correlation is between thyroid hormone in pregnancy and its impacts on neurodevelopment.

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3. In section 3.3.1, the report indicates that NHANES 2007-2012 data for non-pregnant women was used as part of a parameter calibration procedure to simulate population percentiles of fT4, T4, T3, and TSH due to limited data in the range of iodine intake levels of below 75 μg/day. With limited data below 75 μg/day and no data for pregnant women, AMWA recommends that EPA discuss the reliability of this data for use as a calibration for a parameter within the model.

Isolating Perchlorate as the Main Contributing Factor

1. In section 3.5 it is stated that clinical toxicology and occupational studies in high dose subjects showed minimal changes in hormone levels. These populations are not sensitive, nor are they the life stage that the model attempts to study, however, how does EPA explain the lack of a hormonal response at even high doses?
2. This report states that iron deficiency may also cause hypothyroxinemia. A study by Yu et al. (2015) found an association between iron deficiency and isolated hypothyroxinemia in both pregnant and non-pregnant childbearing-aged women, independent of the effects of iodine. A second study (Chang et al. 2013) found a possible correlation between iron deficiency and psychomotor development index (PDI), a factor that two of the studies in this report use to determine the effects of perchlorate exposure. The U.S. Preventative Services Task Force stated in a 2015 report (Siu 2015) that there is little data for the percentage of individuals in the U.S. with iron deficiency. With this in mind, how do you isolate the impacts of perchlorate and account for the possibility of iron deficiency?
3. Figure 5 in section 3.4 (p. 3-13), states the figure "shows that the BBDR model predicts very little difference in non-pregnant and first- trimester response to perchlorate. This likely occurs because the half-life of (organified) iodine in the adult thyroid is around six months, hence the availability of thyroidal iodine in the first trimester pregnant woman is determined to a very large extent by her nutrition and perchlorate exposure several years preceding pregnancy." How does this model account for the possibility that perchlorate exposure's impact on iodine uptake is determined by the years leading up to pregnancy? If considering perchlorate impacts years before pregnancy, how would you exclude other possible factors? AMWA recommends that EPA discuss how these uncertainties impact the reliability and output of the model.

Uncertainties within the Model and Study

1. In section 1.1.2, the report states that the adult thyroid contains several months of T4 stored in the colloid and that it is not expected to see a result in thyroid status in only a two-week study. The five studies selected only looked at thyroid hormone levels at certain points during pregnancy. Some only used hormone values taken at one point during gestation. AMWA recommends that EPA discuss how much uncertainty this brings to the model's output.
2. The report states that the relationship between fT4 and neurodevelopment is still very much evolving. AMWA recommends that the panel discuss the reliability

and certainty of fT4 level impacts on neurodevelopment. AMWA also recommends that EPA discuss any variations in recent findings related to the relationship between fT4 levels and neurodevelopment.

3. Of the five studies used with the model, only two assessed iodine status. With the large impact that iodine has on thyroid hormone levels, AMWA recommends that EPA discuss how much uncertainty this lack of data brings into the results of the report.

4. The populations from the studies used with the model are not from the US, but instead are from the Netherlands and Italy. The report says there is no reason to believe that the impact of fT4 would vary by country unless there is a substantial difference in iodine intake and that three studies showed that iodine intake was similar between the Netherlands and the US. How sure is EPA of this statement, in particular in light of the case studies reviewed, as only two gave data on iodine status? Does EPA have more data to support this postulate?

   Are there other environmental factors that could be influenced based on geographic location? In particular, how does the Vermiglio (2004) study, one of the five studies used, which is in northern Sicily, compare to iodine levels in the U.S.? Two studies (Andersson, Karumbunathan, & Zimmermann 2012; Lazarus 2014) looked at trends in iodine deficiency and found that Europe tended to be iodine deficient, accounting for over a third of the iodine deficient countries in the world, and that the U.S. was, as a whole, iodine sufficient. Zimmermann's 2012 study specifically stated that Italy was iodine deficient including within the pregnant population. Although this study did mention that the Netherlands, where the other four studies have occurred, had levels of iodine within pregnant women that was deemed sufficient.

   AMWA recommends that EPA discuss the possible uncertainties and bias that this assumption brings into the study.

5. The model was limited to using fT4 levels at 12-16 weeks gestation based on a recommendation from the Science Advisory Board (SAB) during the initial review of the model. In section 2.6, the report states that fT4 levels aren't as impactful after 16 weeks, but are still involved in some measure. AMWA recommends that EPA discuss in more detail how much impact fT4 levels can have past 16 weeks gestation and how this might impact the results of the study in relation to neurodevelopment.

6. In section 6.5.2 (p. 6-16) it is stated that "it is difficult to ascertain the true implications of a change in the standard deviation of reaction time, the endpoint with which there is a significant association with maternal fT4 levels." If the implications are so uncertain, why use this study? AMWA recommends that EPA discuss how this uncertainty may impact the interpretation of the results of the report.

7. In section 6.5.5 (p. 6-18) it is mentioned that thyroid tests have yet to be standardized, but that this shouldn't pose a problem "because all individuals in the papers were assessed using the same techniques, any bias resulting from this

source of uncertainty would likely be random and would tend to bias toward the null." This appears to suggest that the same tests are used within each single study, but not necessarily throughout all five chosen studies. AMWA recommends that EPA explain why using different tests among studies wouldn't bring any uncertainty to the results.

8. One study that is referenced for showing significantly increased adverse health affects, particularly in regards to IQ (Taylor et al. 2014, p. 4296) explicitly states in the paper that their "results should be interpreted with caution and analysis viewed in the context of hypothesis generation, although the observed deleterious effects principally on VIQ are in keeping with a recent study of maternal iodine deficiency and subsequent offspring cognitive development. We would not recommend action on perchlorate levels from this study alone, although our report highlights a pressing need for larger studies of perchlorate levels from the general pregnant population and those with undetected hypothyroidism. Future studies should utilize samples taken at several stages of pregnancy with subsequent neonatal thyroid function and more detailed cognitive development of offspring, in particular VIQ." VIQ meaning verbal IQ.

   In light of the author's recommendation, AMWA recommends that EPA discuss whether or not the science has come far enough since this study to make a conclusive determination that perchlorate has an effect on IQ in offspring, particularly since hormone levels are only being considered during weeks 12-16 of gestation.

9. Three of the studies (Pop et al. 1999; Pop et al. 2003; Vermiglio et al. 2004) all had very small sample sizes at 22, 57, and 27 individual children respectively. In comparison, the other two studies used significantly larger sample sizes at 3,839 and 1,765. AMWA recommends that EPA discuss the reliability of the conclusions for the three smaller studies.

Possible Bias

1. In section 5.1, the literature review procedure is discussed. It is mentioned that "search strings" were used in order to find studies that may work best within the model EPA has created (i.e. neurodevelopment AND hypothyroxinemia; hypothyroxinemia AND autism; etc.). AMWA recommends that EPA discuss the biases, if any, that this method brings into determining the effect of hypothyroxinemia on neurodevelopment.
2. The procedure utilized to determine which studies were to be used were only ones that found significance between fT4 and neurodevelopment, the reasoning for this being that only these studies would work within the model. In section 6.5 (p. 6-14) the report states, "one global uncertainty in this analysis is that the state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving." AMWA recommends that EPA discuss the biases introduced into this report by only using these five studies and the method utilized to select them.

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3. Hypothyroxinemia is defined in the report (p. 2-4) by the Science Advisory Board's definition of "a variety of cutoffs….ranging from fT4 below the 10th or 5th percentiles to below the 2.5^{th} percentile." This report used the 10th percentile. According to Dosiou and Medici (2017, p. R24), "there are substantial differences in the definition of IMH between studies, which significantly affect the interpretation of prevalence data for this condition." Why was the 10th percentile chosen? When looking at the "shift" of women who become hypothyroxinemic due to perchlorate, how might these numbers be different if using the 2.5^{th} percentile? AMWA recommends that EPA discuss the biases, if any, this may bring to the report.
4. Different neurodevelopment measurements are used with the model; two studies look at PDI, two look at IQ, and one looks at reaction time. As a whole there are five studies, but in actuality there are three different unknowns between them. This inherently leaves smaller sample sizes for each parameter and, as discussed above, some of these data sets are already quite small. With the amount of data on each single factor, AMWA recommends that EPA discuss whether or not there is enough data to support the findings and if more studies should be analyzed before drawing a conclusion.

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The Chlorine Institute

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November 20, 2017

U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

Re: Comments on the Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (82 FR 43354, EPA–HQ–OW–2016–0438)

Dear Sir or Madam:

The Chlorine Institute ("CI" or the "Institute") is a 190 member, not-for-profit trade association of chlor-alkali producers worldwide, as well as packagers, distributors, users, and suppliers. The Institute's mission chemicals, namely chlorine, sodium and potassium hydroxides, sodium hypochlorite, the distribution of vinyl chloride monomer (VCM), and the distribution and use of hydrogen chloride, are used throughout the U.S. economy and are paramount to the protection of public health.

The Chlorine Institute would like to submit the following comments to the United States Environmental Protection Agency's (EPA's) recent request for public comment on the "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water'' (draft MCLG Approaches Report) Volumes I, II, and III as noted in the September 15, 2017, Federal Register notice (FRN, 2017).

Epidemiology Data Used in the Model: The data used to establish parameters for the model, calibrate the model, and validate the model relies heavily on epidemiology data in early pregnancy. While we agree that an extension of the model to include early pregnancy would be

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beneficial to capture a vulnerable time of brain development and the impact of perchlorate on thyroid hormones, the quality of the available data should be highly considered and evaluated. Epidemiology, focused on human populations, is heavily biased with confounding factors that can impact the effects of perchlorate on thyroid hormone levels, as noted throughout the current draft document. Confounding factors that are difficult to control in human epidemiology studies include identification of smokers, diet, previous disease status, dietary supplement intake etc., all of which can impact levels of thyroid hormones and perchlorate exposure. EPA does not provide justification for excluding pertinent animal studies such as that by Mahle et al., (2003) in which pregnant rats were administered perchlorate in drinking water from gestation day 2 and thyroid hormone levels were measured. Animal studies may provide useful data that have been conducted in well controlled environments with less genetic variability. In fact, Clewell et. al., (2003) developed and published a PBPK model in rat modeling fetal perchlorate dose and inhibition of iodide kinetics during gestation.

Literature Review - Group 1 Study Selection. It is unclear why EPA chose to not include studies with results that were not statistically significant in the association between fT4 and neurodevelopment outcome. These studies would add value in determining hormone levels during pregnancy and neurodevelopment outcome (Ghassabian et.al., 2014; Modesto et.al., 2015; Moleti et. al., 2016; Noten et.al., 2015; Oken et.al., 2009; Velasco et. al., 2009) EPA's reason, for example, for not including the data form the Noten et. al. (2015) paper states that "statistical significance was lost after controlling for confounders" (EPA, 2017, Section 6.0, Table 22). Without taking into consideration studies in which no neurodevelopmental effects were found, creates a bias within the model and therefore the model lacks robustness in informing derivation of an MCLG.

Failure to address other goitrogens in the model. The lack of consideration of other goitrogens such as thiocyanate, which has been shown to compete with perchlorate to inhibit NIS and also is a competitive substrate for thyroid peroxidase, the enzyme required to form T3 and T4 from thyroglobulin and iodine (Steinmaus et al., 2007; 2013), can lead to uncertainty in the model results. It is not enough to justify the lack of consideration and effect of other goitrogens by saying that the model simulates mothers with low iodine intake and low baseline fT4 which addresses the sensitivity to high exposure of other goitrogens (EPA, 2017, Section 3.5, page 3-

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15). Additional data should be considered in the model of how other goitrogens can alter availability of thyroid hormones as well as iodide's interaction with the NIS.

Further, the model assumes that exposures to perchlorate and other goitrogens vary independently in the population and that the effects are additive (EPA, 2017, Section 3-5, p.3.17). The assumption that the effects are "additive" should be further evaluated and clarified. As noted above, other goitrogens can have additional effects on the thyroid hormones that are not consistent with the perchlorate mode of action. Making the wrong assumption on this point can greatly impact the predictions of the effects of perchlorate on neurodevelopment.

Therefore, EPA cannot ignore the effects of other goitrogens on the transport of iodine into the thyroid. Pursuant to Section 1412(b)(4) of the Safe Drinking Water Act (SDWA), the Maximum Contaminant Level Goal (MCLG) "shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." In order to meet this obligation, all goitrogens should be considered in the PBPK model rather than focusing solely on one goitrogen.

Variable expression of the NIS gene. As EPA states, "The degree to which there is inter-individual variation in NIS structure and/or regulation contributing to variance across the population in the impact of perchlorate exposure on thyroid function is currently unknown" (EPA, 2017, Section 3.5, p. 3.16). As supporting data that variation in the NIS gene exisits, EPA sites a paper by Al-Rasheed et al. (2015) who identified variations in the NIS gene that could lead to development of differentiated thyroid cancer. This data indicates that variability in the expression of the NIS gene could render some individuals more or less sensitive to exposure to all goitrogens. This variability, while it has been recognized as an uncertainty within the model, should be considered within the parameters of the mode.

Limited data on toxicokinetics and toxicodynamics of perchlorate. EPA does acknowledge there is limited data on the effects of perchlorate on circulating hormone levels needed for the model (EPA, 2017, Section 3.5, p.3-16). It is noted that clinical toxicology and occupational studies show minimal changes in the thyroid hormone levels (Braverman, et. al., 2007). Epidemiology studies with low exposures, however, show associations between urinary

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perchlorate, increases in TSH and decrease in T4 (fT4) (Blout et al., 2006, Braverman et. al., 2007, Steinmaus et. al., 2016). The lack of toxicodynamic and toxicokinetic data, especially during pregnancy, could impact the prediction of fT4 on neurodevelopmental outcomes. This puts the validity of the model at question. Additional studies should be conducted to increase the validity of the model if using the model to influence and set regulatory standards.

Incorporation of the TSH feedback loop. TSH levels do not have a consistently predictable impact on T4 levels according to Fitzgerald et. al., (2016), due to interindividual variations including genetics, subclinical thyroid disease, age, and gender. The model does account for some of the variability and does make an association between weak responders and strong responders however, not within a fixed set-point. It is important to point out that the whole HPT feedback loop is tightly controlled and that homeostatic set points will vary among individuals. Within this discussion EPA points out that "any exposure to perchlorate is predicted to reduce fT4" (EPA, 2017, Section 3.4, p.3-17). However, a no observed adverse effect level (NOAEL) was established in humans at 7 μg/kg/day in which perchlorate inhibition of radioiodine uptake by the thyroid (Greer et. al., 2002) (EPA, 2017, Section 3.4, p. 3-14). In fact, EPA incorrectly cites this level as the NOAEL but Greer et al, 2002, cite this level as the No Observed Effect Level (NOEL), the level at which no statistically or biologically significant increases in the frequency or severity of any effect is observed. This clearly indicates there is a dose at which perchlorate does not impact iodide uptake by the thyroid and therefore fT4. This statement should be changed to reflect the dose-response of perchlorate on fT4 levels. In additional, perchlorate acts on the NIS to alter iodine levels, not directly fT4 levels. The model's only output being considered is the effect of perchlorate on free thyroxine (fT4) and no other measures of thyroid function. To understand the complex feedback and homeostatic mechanisms in the hypothalamic-pituitary-thyroid axis, several measures of thyroid function should be modeled, including, T3, T4, TSH, thyroglobulin, and thyrotropin releasing hormone.

Determining Distribution of fF4. The literature review suggests that gestational weeks 12, 13 and 16 were best to focus on and further that the fT4 is best to assess in order to calibrate the model for the median-iodine intake. However, the data is very limited at these time points during gestation. Specifically, Li et. al., 2014), Männistö et. al., 2011), and Zhang et. al., 2016) were evaluated for weeks 12 and 13. Only Männistö et. al., 2011) and Zhang et. al., 2016) were

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evaluated for week 16. Only one study evaluated week 13 (Männistö et al., 2011). Further it is difficult to determine whether the lognormal distribution can be applied versus a normal distribution with such limited data. Additional data should be considered at additional gestational timepoints in the first trimester (EPA, 2017, Section 4.1, p. 4-1). Perhaps the studies that measured levels of fT4 at various gestational time points in Group 1 of the literature reviewed but were disregards by EPA as not having statistical significance could be helpful here.

Failure to address compensation and adaptation. Critical assumption for concern in the model is that there is no compensation or adaptation of thyroid hormones, levels of iodide, or changes in expression of the NIS considered. As noted already, homeostatic control of the HPT axis, iodide intake and gene expression of NIS are all variable and as such compensatory mechanisms or mechanism of adaptation to varying levels of thyroid hormones, iodide and NIS expression should be included in the model to more accurately reflect the effects of perchlorate on neurodevelopmental outcomes.

Neurodevelopmental endpoint selection. It is unclear why EPA selected ADHD and autism in their literature search as neurodevelopmental endpoints to assess the effects of iodine on thyroid hormone levels (EPA, 2017, Section 5, page 5-1). These are not appropriate endpoints given the spectrum of both diseases. The literature review should focus on studies in which measurable and clearly defined endpoints in the study are reflective of neurodevelopment outcomes.

In addition, neurodevelopment can be affected by many different types of exposure scenarios. A single measurement of thyroid hormone in the first trimester of pregnancy cannot predict neurodevelopment in offspring at one year after birth and up to 10 years after birth. During this period, there are many factors that could affect brain development.

Alternative Approach (Section 7.0). EPA cites that an "alternative option to inform future decisions on the derivation of an MCLG using the BBDR model is to evaluate a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate" (EPA, 2017, Section 7, page 7-1). However, EPA indicates this approach does not directly connect the BBDR output to neurodevelopment. It appears the approach is to be preventative in that the shift could prevent an increase in "risk" to the neurodevelopmental impacts of low thyroid hormone levels based on EPA's literature review of hypothyroxinemia

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and adverse neurodevelopmental outcomes. However, the data used in the model should link to neurodevelopmental outcome; otherwise the model will not meet the goal of assessing the effects of perchlorate on neurodevelopment.

In addition, it seems that this approach would increase uncertainty in individual fT4 measurements within a presumed smaller population size. A single fT4 measurement may represent hypothyroxinemia for one individual at a certain time point, but not for the same individual at a different time point or for another individual (EPA, 2017, Section 7.0, page 7-5). There is an assumption that neurodevelopment deficits would occur however, the data does not measure neurodevelopmental outcomes. Again, without the proper data being input into the model, the validity of the model is questionable, rendering the model not useful.

Appendix C: Comparison of the BBDR model with the Steinmaus et al. Data - Change in IQ: In Appendix C of Volume III, EPA makes a comparison between the Steinmaus et. al., (2016) data of urinary perchlorate and fT4 levels in women in urine at 7 weeks of gestation and in blood at 15-20 weeks of gestation to the results of the BBDR model and states that the results of the model indicate it would take 2.91 µg/kg/day to cause a 1 point change in IQ. However, the results of the Steinmaus et. al., (2016) study are only based on one collection time point for each pregnant woman and it appears to be a big assumption that 1 point change in IQ can be determined by one time point in one study.

Independent Review Recommended Prior to Completion. As the model nears completion, it is essential that an independent, third party evaluation and validation of the model be conducted to understand the completed models' strengths, weaknesses and what further improvements may be required of the model before using the model to inform a MLCG for perchlorate.

In conclusion, EPA has made great strides in improving the draft PBPK model to inform a MCLG for perchlorate. However, there are still many limitations of the draft PBPK model that need to be addressed, including the lack of data to calibrate and validate the model specific to sensitive life-stages. We encourage EPA to select peer reviewers with the expertise to evaluate all facets of this model with the understanding that it will be used to inform MCLG which, in turn, will influence global regulatory standards.

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Thank you for the opportunity to comment and your consideration of our requests.

Sincerely,

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Department of Defense

Comment submitted by the Office of the Deputy Assistant Secretary of Defense, Environment, Safety and Occupational Health, US Department of Defense

The is a Comment on the **Environmental Protection Agency** (EPA) Notice: **Requests for Comments: Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate**

For related information, **Open Docket Folder**

Comment Period Closed
Nov 20 2017, at 11:59 PM ET

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Comment

Please see attached comments provided by the US Department of Defense.

Our comments submitted by the Office of the Deputy Assistant Secretary of Defense, Environment, Safety and Occupational Health focus on concerns associated with the lack of systematic review of the literature to support linking clinical data ofdevelopmental effects and low T4 thyroid hormone and the lack of a description of how negative studies were or were not considered in the literature search. We also provide comment and highlight our concern with the additional approach included in the report which is not
based upon developmental effects but rather a population shift towards hypothyroxinemia given exposure to perchlorate. The rationale for inclusion was not described and there are particular technical aspects of it
are troubling, such as a change in perchlorate baseline from the original study whose effect is a significant change in hormone levels, beyond that seen in the original (Steinmaus).

We appreciate the opportunity to provide comment on the technical report and look to EPA to ensure that the peer review panel charge questions address these and any other remaining technical issues with the report.

Attachments (1)

Comment

View Attachment: PDF

Department of Defense Comments on
Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

Comments submitted by: OASD(EI&E), ESOH	Organization: Department of Defense	Date Submitted: 11/17/2017

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	1.1 Background on Perchlorate	1-1	The text states: "However, the main source of perchlorate currently in the environment is from the production and usage of rocket fuel, by both the defense and aerospace industries (NRC, 2005)." The statement seems outdated, since 2005 several reports have been published that point towards fireworks as contributing to perchlorate in the environment.	Please see and consider Sijimol, MR, "Environmental Impacts of Perchlorate with Special Reference to Fireworks", Environmental Monitoring and Assessment, Nov 2014, vol. 186, pgs 7203-7210.	S
2	2.1 Overview of Thyroid Physiology	2-1	The document states that "T4 is generally thought to act as the prohormone for the more biologically active T3... However, it should be noted that the regulatory factors that modulate the delivery of T4 to the fetus are not fully understood." As EPA is using T4, and not the active T3 in its BBDR model, it is not clear how free T4 can be accurately estimated without this knowledge.	If T3 is the entity that determines effect on development in the fetus, EPA should clarify why it chose to use fT4 as the metric.	S
3	2.1 Overview of Thyroid Physiology	2-1 & 2-2	As noted in comments on Appendix B, EPA acknowledges that selection of the "set-point"	EPA needs to not only more completely justify its selection of the set-point used, but also, and	S/M

			will significantly affect the results of the model. Here, EPA states "different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance ..." Yet the set-point appears arbitrary and definitely does not account for the large variance described in this text.	more importantly, needs to provide information on the effect of using a single value, rather than a range for the set-point, as indicated by the information presented in this paragraph.	
4	2.1 Overview of Thyroid Physiology	2-2	"It is generally thought that" plus citing one partial example does not support the hypothesis.	If it is indeed generally thought, then either a review article or a text book citation should be available and should be cited. If not, suggest that this paragraph be deleted as it would not be sufficiently scientifically supported.	S
5	2.4 Perchlorate's Impact on Thyroid Physiology	2-6	The NIS km for perchlorate is 60% of that originally predicted and the rationale is provided. However, simulations of the improved fits of radioiodide uptake in thyroid are not provided.	To lend some transparency, please provide some simulations of inhibition of radioiodide uptake in the thyroid from Greer et al. (2002) or other studies.	S
6	2.4 Perchlorate's Impact on Thyroid Physiology	2-6	Since EPA states that "PCBs, polybrominated diphenyl ethers (PBDEs), bisphenol A, and perfluorinated acids (PFAs), also disrupt thyroid homeostasis", it is important that the document clearly state if the data used in the PBPK model appropriately accounts for potential exposure to these confounders.	As there is wide-spread and variable exposure to the chemicals named, and as EPA notes that co-exposure, e.g., smoking, can cause synergistic effects, it is important that the data used to estimate dose-response effects be adjusted for these exposures or the variability acknowledged to the extent possible.	S/M
7	2.5 Distribution and Excretion of Perchlorate	2-27	Relying on inferences from recent, apparently not replicated, in vitro studies EPA infers that "if this is the case, additional stimulation by maternal TSH in the presence of perchlorate may result in an absolute increase in NIS and	Since as the document states, "there is no direct evidence to indicate that the quantity of placental NIS is upregulated in response to increased TSH", EPA should qualify the conclusions from its model with this caveat.	S

			subsequently increase perchlorate transfer to the placenta."		
8	3 Overview of EPA's Biologically Based Dose Response Model	3-1 - 3-18	Plasma protein binding may be contributing to fT4 remaining extremely low, while the pituitary is still producing normal TSH levels under hypothyroxiemia. Under normal conditions, 90% of plasma bound iodide is T4 and approximately 5% is T3 (Berkow et al., 1977). Plasma inorganic iodide is about 0.4 +/- 0.23 ug/dl (Elte et al.,1983). Dissocation of free iodide involves both deiodination and dissociation from serum proteins. It appears that a fraction of total iodide and THs were applied to distinquish these concentrations.	Please clarify how plasma protein binding of iodide or thyroid hormones were handled and what limitations the approach has for simulating altered fT4. Describe if a constant percentage was used.	S/M
9	3.1 Background and Structure of BBDR Model Development	3-3	Since Lumen and George have updated their model, it would seem reasonable to (1) note any differences between EPA's changes and those of the authors of the model, and (2) determine if the two versions provide reasonably similar results.	Since two models are available, both should be utilized to at least some degree. This is especially important if any parameters were changed in the 2017 Lumen and George analysis, as "Table 1. Summary of Major Features of Current BBDR Modeling" only discusses parameters from Lumen et al. (2013). This analysis should reflect the current state of the art.	S
10	Background and Structure of BBDR Model Development	Figure 4	Much work has gone into development of this report and in the process, the BDDR model has been simplified in some respects from the previous version and enhanced in others (such as the TSH feedback). The fetus and placenta were lumped with the "rest of body"	Include the fetus and placenta in the model and predict the effect of perchlorate on total fetal iodide. If this has already been done during earlier revisions, please discuss the outcome and why it was abandoned.	S/M

			compartment because their volumes are too small to affect the evaluation of sensitive parameters. However, the fetus is the endpoint. Data are extremely limited for these "tissues", but fetal and placental iodide concentrations were simulated in Clewell et al., 2007 and calibrated aginst data of Aboul-Khair et al. (1966); Dyer et al. (1969); Dyer and Brill (1972). It is true that the small volume of the fetus and placenta will not likely impact on perchlorate or iodide kinetics in the mother, but their inclusion would allow us to evaluate the parameters to which the fetus is most sensitive.		
11	3.3 Overview of Key Model Attributes	3-8 and Table 1 on page 3-7, first box	hCG may play a much larger role in T4 production than is mentioned here.	Please provide more information about its potential involvement with T4 production than one sentence in a Table with a reference.	S
12	3.4 Results of the BBDR Model	3-10	In the footnote, there is an "l" missing from "Lambert-Meserlian et a."	Please correct.	E
13	3.4 Results of the BBDR Model	3-10	Given the recommendations in the footnote on this page, it is difficult to understand why EPA chose to only evaluate fT4 in its modeling. The American Thyroid Association's recommendation to use TSH post-date those of EPA's SAB, and should be considered to have some authority.	Since the BBDR model must have also calculated the TSH concentrations for all of the runs that produced fT4 concentrations, we strongly recommend that these data be provided to the public. Even if EPA does not choose to use these data, based on the recommendations of the ATA, other stakeholders may wish to use those data to analyze the effects of perchlorate.	S/M

14	Figure 5 Example Output from the BBDR Modela	3-11	For fT4, there should be an explanation as to why, when the median and lower bound change so much, that the upper bound changes only a little and only at the highest doses. For TSH, we note that only the lower bound changes significantly. The lack of change in the upper bound, and for TSH in the median, suggests that conditions were selected that are sub-optimal for determining the range of iodine status that might be affected by exposure to perchlorate.	Suggest that more data points would improve the knowledge for the decision-maker.	S/M
15	Figure 5. Example Output from the BBDR Modela	3-11	As currently formatted, the key for the 4 graphs in this figure blocks some of the data.	Please move the key.	E
16	3.4 Results of the BBDR	Tables 2 and 3	Both tables require checking and review in order to provide accuracy, clarity, and transparency.	Each issue will be addressed in a separate comment.	S/M
17	3.4 Results of the BBDR	Table 2	Although this comment may be due to rounding errors, we note that, with the exception of the final value, the penultimate column has exactly the same (to 3 figures) concentration of TSH, but the percentage change ranges from 0.04 to 0.21.	If the data can support more than 3 significant figures, they should be provided. If the data cannot support 4 or more significant figures, then the percentage change is scientifically meaningless and should not be presented.	S
18	3.4 Results of the BBDR Model	Table 2	It is not possible to check the percentage change in the penultimate column for most of the values, as the data presented do not allow for this calculation. For the highest calculation, however, and assuming the usual definition of percentage change, i.e., [(1.36 - 1.35)/1.35] x 100 = 0.74 not 0.45 as in the table.	All of the calculations in Tables 2 and 3 should be validated to ensure the values are accurate.	S

19	3.4 Results of the BBDR Model	Table 2 and 3	It is unclear if the changes reported in these table represent a change that is biologically or clinically significant, or whether the estimates are within the range of normal women, pregnant or not.	Percentage change from control does not necessarily represent an adverse effect. For clarity and transparency, the document should provide information as to whether these changes are biologically or clinically significant. We assume they are not statistically significant, or that fact would have been reported.	S
20	3.4 Results of the BBDR Model	Tables 2 and 3	The number of significant figures in these tables is not consistent. In Table 2, fT4 is reported to 4 significant figures, while in Table 3, only 3 significant figures are reported. Assuming the data and analyses are the same, the number of significant figures reported should also be the same. As it is, the number of significant figures reported appears to have been selected to demonstrate a change rather than whether the underlying data support that change. The number of significant figures for percentage change in Table 2 range from 1 to 2; in Table 3, from 2 to 4. First, since only 3 significant figures are presented in the data for Table 3, any further analysis cannot support more than 3 significant figures.	The number of significant figures reported should accurately reflect the precision of the data and the analysis applied thereto. From this presentation, it is unclear if the underlying data support these minimal differences, or if the "changes" may be due to either "noise" in the data or lack of appropriate truncation of the data.	S/M
21	3.4 Results of the BBDR Model	3-13	The substance of the paragraph below Table 3 includes important information and should be included in the Executive Summary.	Since the focus of this analysis is on the first trimester of pregnancy, suggest adding a sentence such as: "During the first trimester, the BDDR model predicts little change in the percentage drop in fT4 or percentage increase in TSH due to perchlorate exposure, although	S/M

				baseline TSH and total T4 levels do vary significantly with gestation".	
22	3.5 Uncertainties Associated with the BBDR Model	3-15	To improve clarity and transparency, it would be useful if there were citations provided to support the following statement: "While the BBDR model does not explicitly consider other goitrogens (e.g., thiocyanate, nitrate), simulating results for a mother with low iodine intake and low baseline fT4 may help to address the sensitivity of individuals with high exposures to other goitrogens."	Since the assumption that perchlorate and other goitrogens are (1) fungible with each other and (2) compete with iodine only based on their Km, it would seem that this statement should be qualitatively and quantitatively supported beyond the assumption.	S
23	3.5 Uncertainties Associated with the BBDR Model	3-17	The following statement is inconsistent with EPA guidance, guidelines, and standard practice that assumes a threshold for non-cancer, adverse effects: "Any exposure to perchlorate is predicted to reduce fT4 to some extent." It is also inconsistent with the statement on page 3-14, "This result is consistent with the underlying Greer et al. (2002) data in human test subjects, which showed a no observed adverse effects level (NOAEL) for perchlorate inhibition of radioiodide uptake by the thyroid NIS of 7 Âµg/kg/day."	Please reconcile and correct.	S
24	3.5 Uncertainties Associated with the BBDR Model	General	The discussion of uncertainties associated with the model is vague in terms of their meaning for protection of public health and is also lacking in terms of quantitative analysis.	Please more clearly discuss whether the uncertainties would tend to underestimate or overestimate threats to the population. If there was a sensitivity analysis performed please describe. In the case of the last paragraph where thyroidtitis is discussed please note	S/M

				whether this was a sensitive subpopulation suggested by the SAB panel or otherwise describe its relevance for purposes of the MCLG determination.	
25	4.1 Evaluation of Distributional Shape and Derivation of the Geometric Standard Deviation		It is neither clear nor transparent why EPA chose to develop a complex model and then not use the model to estimate all of the data in tables 6, 7, and 8. Presumably, the analyses that produced the median that was derived (according to the footnotes) from the model could have also generated the other percentiles of the distribution generated. By only using the median and not the other percentiles, this more complex process (of estimating GSDs from variable data) suggests that there is a problem with the model for all percentiles other than the median.	If the model is only considered accurate for estimating a median, this should be clearly stated and the "problems" with estimating the other percentiles should be discussed. If the model is considered accurate for the other percentiles, those data should be presented. In either case, the "predictions" in these tables based on a weighted, estimated GSD should be compared with the results of the same conditions with the BBDR model.	S/M
26	4.1 Evaluation of Distributional Shape and Derivation of the Geometric Standard Deviation	4-1	This section states that it was a review of the literature that caused EPA to focus on T4 rather than TSH. However, the referenced chapters appear to stress that it was the comments and recommendations of the SAB that cause the switch from TSH to T4. Indeed, EPA's most recent, authoritative reference, i.e., that of the ATA (2017), suggests use of TSH as the metric.	Please clarify, and provide references in this discussion, as to which papers were decisive in EPA's move to T4.	S
27	4.1 Evaluation of Distributional Shape and Derivation of the	4-1	Neither skewness nor that "lognormal function demonstrated a better fit than a normal distribution" are reasons to assume that the distribution is truly lognormal. It would seem	With existing computer power, it is no longer necessary to force distributions to be normal or lognormal. While the analysis is more complex, establishing MCLGs that will lead to regulatory	S/M

	Geometric Standard Deviation		more likely that the distribution is bimodal, i.e., that there is a normal population and a secondary population that is, for whatever reason (genetics, other exposures), low in thyroid. While a bimodal distribution is admittedly more complicated to evaluate, methods exist. For example, random sampling for the BBDR model can be done from a distribution based on data rather than one artificially forced to be lognormal. The method provided in footnote 8 is at best a subjective judgment. Use of Excel for statistical analyses limits the quality. EPA has statisticians with access to statistical software that can perform a more rigorous analysis of these data. This analysis should not be limited by the lack of statistical knowledge of the authors of the document.	MCLs should rely on best statistical practice, not that which is most facile.	
28	4.3 Limitations and Uncertainties of Method	4-6	As the two studies used to select the parameters for the analyses in chapter 4 to this point disagree on the distribution and as the previous comments demonstrate additional limitations of the approach used, it is critical that EPA justify their approach as it appears to be not supportable by the data presented.	If the combined data are neither normal nor lognormal, the distribution should be evaluated based on the empirical data points. If, as suggested here, one data set favors a normal distribution while another favors lognormal, the data should be analyzed both ways to determine if the difference in results is sufficient to continue with both analyses. If these analyses are to form the basis for an MCLG leading to a regulatory MCL, EPA should not arbitrarily select one of two or more options that may lead to quite disparate values for the MCL without a strong, scientific justification that is clearly lacking in this case.	S/M

29	5.2.2 Step 2. Categorize the Remaining Studies	5-3	Since it is unlikely that any study measured maternal hormone levels daily, much less throughout the day, for all of the months of pregnancy, "a continuous measure of maternal thyroid hormone levels" is highly unlikely.	Here and elsewhere, suggest replacing "continuous" with "repeated measures", or otherwise define how “continuous”.	E
30	5.3 Results of Evaluation to Identify Studies That Directly Relate Thyroid Hormone Levels with Neurodevelopment	5-4	The following statement suggests that studies that found that exposure to perchlorate as not associated with neurological effects were ignored in this analysis: "As presented in Figure 6, the literature review identified 55 studies that link thyroid hormone levels to neurodevelopmental effects." Negative as well as positive studies must be examined to provide an unbiased analysis.	Please describe how any studies that did not find an association between perchlorate exposure and neurodevelopmental effects were evaluated.	S/M
31	5.3 Results of Evaluation to Identify Studies That Directly Relate Thyroid Hormone Levels with Neurodevelopment	5-5	Since the BBDR model assumes a quantitative relationship between TSH and fT4, it is not clear why "if the study only had data on TSH" should matter.	Please clarify.	S
32	6 Informing the Derivation of an MCLG: Neurodevelopmental Effects	6-1	It is not clear how the tables of estimated changes in neurodevelopmental outcomes in relation to fT4 and iodine intake are intended to be used by EPA. The first paragraph of the section states "This section demonstrates how EPA could inform the derivation of an MCLG for perchlorate by evaluating how various doses of perchlorate to a pregnant woman may result in	Please describe the intent of the data derived from the analyses and presented in the tables in this section. Please discuss whether they will be combined into a single table or perhaps the outcomes plotted as a function of fT4 and how this may be used to derive the MCLG.	S

			changes in neurodevelopment of her child.", but we see no actual demonstration.		
33	7 Informing the Derivation of an MCLG: Hypothyroxinemia	7-1	The alternative option presented here that uses a shift in the population below the hypothyroxinemic cut point was not suggested by the SAB and is not related to developmental endpoints by EPA in their analysis. It is not clear why it is presented here.	Please clearly describe why this option was deemed necessary for presentation in this document and its purpose for deriving an MCLG.	S/M
34	7 Informing the Derivation of an MCLG: Hypothyroxinemia	7-1	Inclusion of hypothyroxinemia and the alternative option is partially justified by "the preponderance of evidence located in EPA's literature review that finds an association between hypothyroxinemia and adverse neurodevelopmental outcomes." But it is not acknowledged that only a biased search of the literature looking for studies with positive results was performed, there was no systematic review of the literature as is noted in other DoD comments.	Do not use this as a justification to move away from the SAB recommendations unless an unbiased literature search is performed.	S
35	7 Informing the Derivation of an MCLG: Hypothyroxinemia	7-1 - 7-2	This section discusses the results of literature search as if it were nonbiased and would include studies with null results. However, as stated in Section 5.1 a full systematic review was not performed.	Suggest clarifying whether any null results were found and whether the design of the literature search would have precluded them.	S
36	7 Informing the Derivation of an MCLG: Hypothyroxinemia	7-3	The figure and the associated text assume the fT4 versus probability distribution will stay the same during exposure to perchlorate. While this simplifies the analysis, it is highly unlikely. First, the "average" response to a given exposure to	Some reasonable, scientific analysis must be provided if this assumption is to be retained. For example, a selection of initial fT4 values that differ substantially, e.g., the 10th, 30th, and 50th percentiles, should be run through the	S/M

			perchlorate would be expected to depend on the fT4 level prior to the exposure. Second, even with a specified fT4 level, individual responses to the specified exposure would be expected to differ. This is supported by the statement on page 7-5 that "intra-individual variance in fT4 may also be a factor affecting the tail of the distribution, about 10% of the population variance is made up of intra-individual variance (Andersen et al., 2002)." Both of these effects would be expected to spread the distribution as well as shift the median.	BDDR model with the addition of the same amount of perchlorate to demonstrate that the resulting "change" is consistent with the shift in the curve without any change in the shape of the curve.	
37	7.2	7-5	The analysis in this section, and therefore all of the conclusions therein, rely on the assumption that the shape of the distribution of fT4 remains constant during exposure to perchlorate. As mentioned in a previous comment, this assumption is problematic. No scientific justification is presented for this assumption that is counterintuitive.	Please provide a scientific justification or perform BBDR modeling to provide some basis for this assumption.	S/M
38	8.1 Hypothyroidism	8-1	It is stated that, "the human thyroid contains several months of T4 in the colloid". Is this statement based upon the results from Braverman et al. (2006), Laurence et al. (2000), or another study?	Please provide the relevant citation.	S
39	8.3 Other Potential Diseases	8-2	EPA states that the Comparative Toxicogenomics Database (CTD) has identified 455 diseases potentially assocated with perchlorate, but provides no discussion of what	Please describe the CTD findings more fully.	S

			those possible mechanisms of action are other than NIS inhibition or oxidative damage.		
40	9	Table 39	According to the equations on 6-6 and 6-7, as well as the discussion of the regression analysis, it appears that all analyses were of the ln(fT4). If this is an accurate interpretation of what was done, the last column of this table is either labeled incorrectly or is misleading or both. At best there is a linear relationship between the natural logarithm of fT4 and dose of perchlorate, in which case the "Dose of perchlorate per unit change in endpoint" will be highly dependent on the level of fT4 prior to the exposure to perchlorate. Thus, presenting the values in this column as a constant is inaccurate, as well as neither clear nor transparent. If the conclusions could be accurately portrayed in a table as simple as this one, we wouldn't need a BBDR mode.	Attempts to provide a simplistic conclusion to a complex analysis, such as those in Table 39, can be expected to be misinterpreted and misapplied by anyone who does not read and fully understand the complete document with all appendices. Especially the final column that implies a linear relationship between dose of perchlorate, change in fT4, and therefore, neurological effects, is simple, and simply incorrect. While such numbers can always be "calculated", the conditions that must apply in this case would take pages to describe. Therefore, without these qualifications, the table could be described as misleading or deceptive.	S
41	9 Conclusion	9-1	Stating: "the majority of studies identified support the notion that avoiding a shift in the proportion of the population at risk of hypothyroxinemia may avoid adverse neurodevelopmental outcomes" to justify this approach is not valid when the literature search was designed with this bias to find studies with positive results. See related comment above.	Please revise.	S
42	9. Conclusion	9-1	The following statement not consistent with our observations of EPA practices and our	Please correct or cite the guidance that describes the “more common approach”.	S/M

			knowledge of their guidance: "This is opposed to the more common approach of exploring the effect of a contaminant on a mean individual from a sensitive life stage." Per the EPA Benchmark Dose Guidance dated 2012 the practice is to use the lower confidence bound on a low response level, e.g., BMDL10 or BMDL5%, as the point of departure. The dose-response function used for this POD is usually that which either is or includes the most sensitive population. The mean, or more often the median, may be used when data are transferred among models, e.g., from the rat PBPK model to the human PBPK model, as it is the most certain and most stable data point. A much lower response is used from the final model.		
43	Appendix B	B-1	EPA has mentioned in the main document that the first trimester of pregnancy is the critical window in development in which thyroid hormones play a critical role. Steinmaus et al (2016) measured thyroid hormones in the second trimester approximately 8 to 13 weeks after their initial measurements of urinary perchlorate. The regression analysis by Steinmaus demonstrated the negative correlation of 1st trimester perchlorate urine levels with 2nd trimester fT4 and T4 but a positive correlation with TSH. Table B-2 failed to mention p values for those regressions, however. Perhaps the Project Baby's Breath protocol precluded 1st trimester blood draws.	There needs to be some explanation here of the relevance of second trimester thyroid hormone concentrations when the first trimester has been previously identified as the more critical time point.	S

44	Appendix B	B-4	The document states that the study used for the analysis, i.e., Steinmaus et al. (2016), "did not find a different relationship between perchlorate and fT4 or TSH between low and normal iodine intakes"" and therefore, "EPA calculated changes in fT4 and TSH using the all subjects iodine intake". However, EPA's hypothesis is that only populations that are deficient in iodine will be affected by exposures to low levels of perchlorate. Therefore, the data set that EPA believes is the most robust is in conflict with EPA's hypothesis.	This conflict requires resolution. Though the combined data might be justifiably used to develop parameters for the PBPK model, the fact that the data demonstrate that iodine deficiency does not increase the effects of perchlorate on thyroid hormones inherently conflicts with the modeling effort that describes an effect.	S/M
45	Appendix B	B-5	The beta estimate for the slope of the TSH function here is negative and falls outside of the range of the confidence intervals.	Correct the typographical error	E
46	Appendix B	B-6	EPA here assumes a baseline perchlorate dosage that is higher than the NHANES data but below that of Steinmaus et al (2016). The magnitude of the baseline is shown to have a significant effect on the overall effect of a particular perchlorate dose, but little to no explanation is given as to why the EPA assumes a lower baseline than Steinmaus. The combination of an artificially low baseline produces the "effect" of a change in the hormone levels based on the un-stratified data that was not observed in the analysis of the observed lack of effects of the study selected by EPA as the best data set.	Justification needs to be provided in regards to why this particular baseline was chosen.	S/M

47	Appendix C – Discussion	C-6	Here the case is made that there exists additional, unaccounted-for uncertainties in the relationship between fT4 and IQ. Are such uncertainties not addressed in the underlying literature, Korevaar et al. (2016)? EPA has made no attempt to explain the need for a predictive model between perchlorate exposure and IQ decrement. The effect slope is based on one Dutch study only, and the variability around that crucial beta estimate is quite high. It would be nice if EPA would supply references wherein these models have been previously used to predict adverse neurological effects through an intermediary hormone impacted by other, xenobiotic agents.	Further clarification about what exactly are these additional uncertainties and why they are not adequately addressed in the underlying literature is needed before resorting to Monte Carlo analysis.	S
48	Appendix C - Methods	Table C-5	According to this table, the effect measured by Korevaar et al (2016) is statistically insignificant with a high standard error. This calls into question the usage of fT4 and IQ data from Korevaar et al. (2016) because of the high amount of uncertainty surrounding the relationship between these two parameters.	Suggest that EPA provide an explanation for the use of non-significant effect estimate and how it relates to the inverted-U shape curve found in the original paper.	S
49	Appendix C	General	The premise of this appendix is to relate perchlorate exposure to an adverse neurodevelopmental outcome. In this case, a decrease in IQ of 1 point is considered such an outcome. The change of 1 IQ point does not appear at face value to be a significant effect. Korevaar says in a Dutch study that there's an inverted U-shaped association of maternal	This endpoint/critical effect needs to be evaluated by a developmental psychologist or another appropriate expert because it appears to be insignificant. Additionally, text needs to be included that describes the relative amount of risk associated with this effect, because it may be of more importance to some rather than others.	S/M

			thyroid function during early pregnancy with cognitive function, wherein both low and high maternal fT4 (but not TSH) concentrations during early pregnancy were associated with lower child IQ and lower grey matter and cortex volume by MRI scan. It seems there is an attempt to stretch the syndrome through de novo analysis of the Korevaar et al. (2016) data to say that the perchlorate effects on fT4 are enough to drop IQ by 1 point. But 1 point when the average is 100 would appear to be insignificant and we question the accuracy of measuring such differences. We were not able to include an expert in such measurement and testing in our review team and would defer to other external reviewers with such expertise		
50	General	All	The mechanism of action for perchlorate was determined by the National Research Council in 2005. If there is perchlorate exposure above the threshold for iodide inhibition, there should be no effect. The mechanism of action is being ignored in this report.	Include the mechanism of action in the analysis of hormones levels and neurodevelopment.	S/M

Environmental Defense Fund / Natural Resources Defense Council

November 19, 2017

Samuel Hernandez
U.S. EPA, Office of Ground Water and Drinking Water
Standards and Risk Management Division, (Mail Code 4607M), 1200
Pennsylvania Avenue NW.
Washington, DC 20460;

RE: Comments on EPA's Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water at Docket No. EPA-HQ-OW-2016-0438

Dear Mr. Hernandez:

The Environmental Defense Fund (EDF) and the Natural Resources Defense Council (NRDC) appreciate the opportunity to comment on the Environmental Protection Agency's (EPA) draft report on proposed approaches to inform the derivation of a maximum contaminant level goal (MCLG) for perchlorate in drinking water at Docket No. EPA-HQ-OW-2016-0438-0019.[1] EPA requested comments on the draft report in the September 15, 2017 *Federal Register* and extended the comment period to November 20, 2017 in the October 12, 2017 *Federal Register.*

With this latest analysis, EPA scientists address the central question raised by EPA's Science Advisory Board (SAB) in 2013, commenters (including NRDC and EDF), and the agency's peer review panel: what is the relationship between perchlorate exposure in the first trimester of pregnancy on a child's neurodevelopmental outcomes when the mother gets insufficient iodine in the diet. The issue is critical because almost half of US pregnant women get insufficient iodine, especially in the first trimester when they may not be yet aware they are pregnant and under a doctor's care. The SAB specifically requested that EPA consider the effects of low levels of free thyroxine (fT4), referred to as hypothyroxinemia, that had not resulted in an increase in thyroid stimulating hormone (TSH), rather than hypothyroidism where the low T4 had already triggered an increase in TSH levels.

From their review of literature, EPA scientists stated that:

> [E]arly in brain development, fT4 deficiency can affect neuronal cell proliferation and cell migration in the hippocampus (essential for learning and memory, cognitive function), cerebral cortex (essential for executive function, cognitive function), and the medial ganglionic eminence (transitory development structure responsible for guiding axonal migration) (G. Williams, 2008). Maternal hypothyroidism or hypothyroxinemia at these early stages may result in problems with gross motor skills and visual attention and processing (Zoeller & Rovet, 2004). As the first trimester progresses, increases in hCG [Human chorionic gonadotropin] result in a higher production of T4 and reduced TSH and TBG (Morreale de Escobar et al., 2007). In the fetus this period also corresponds to

[1] EPA Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water, September 2017. See https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0438-0019.

> neurogenesis in the midbrain and cortex, neuronal migration into the cortex, deiodinase activity for conversion of T4 to T3, and presence of nuclear thyroid receptors in the brain (Morreale de Escobar et al., 2004).[2]
>
> Higher levels of maternal fT4 throughout pregnancy allow for normal neuron and glial cell migration and differentiation, axonal growth, dendritic branching, neurogenesis, and synaptogenesis to occur (G. Williams, 2008). The complex interconnectedness of brain regions required for normal function could be impaired by effects on all of these processes simultaneously or in sequence, and across multiple brain regions. Maternal thyroid deficiencies during these processes further affect visual processing, development of fine motor skills, IQ, and selective learning problems (Zoeller & Rovet, 2004; Zoeller et al., 2007).[3]

EPA scientists concluded that:

> Evaluating these results as a whole demonstrates that in different populations, at different ages for neurodevelopmental assessment, and at various cut points for fT4, there is a significant difference in performance on global cognitive tests when comparing the offspring of hypothyroxinemic women to those of non-hypothyroxinemic women (Costeira et al., 2011; Ghassabian et al., 2014; Júlvez et al., 2013; Korevaar et al., 2016; Li et al., 2010; Pop et al., 1999; Pop et al., 2003; Suárez-Rodríguez, Julián, and Aguilar, 2012).[4]

EPA's scientists also highlight that neurodevelopmental adverse outcomes other than cognition have also been found:

> Additionally, studies identified in the literature review . . . also associated maternal hypothyroxinemia with an offspring's increased risk of schizophrenia (Gyllenberg et al., 2016), ADHD (Modesto et al., 2015), expressive language delay (Henrichs et al., 2010) and other outcomes (Finken et al., 2013; Kooistra et al., 2006; Noten et al., 2015; Päkkilä et al., 2015; Román et al., 2013; van Mil et al., 2012).[5]

Based on the targeted literature search, EPA's scientists identified 55 studies assessing thyroid hormone levels and neurodevelopmental outcomes.[6] They narrowed the list to 29 studies, referred to as Group 2, which considered the relevant exposure window and were compatible with the Biologically Based Dose Response (BBDR) developed by the Food and Drug Administration (FDA) and refined by EPA. They further narrowed the list to 15 studies, designated as Group 1, which evaluated fT4 as a continuous or categorical measure. EPA concluded that:

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[2] EPA Draft Report, Section 2.6, pp. 2-8 to 2-9.
[3] EPA Draft Report, Section 2.6, pp. 2-9.
[4] EPA Draft Report, Section 5.4, page 5-56.
[5] EPA Draft Report, Section 5.4, page 5-56.
[6] EPA Draft Report, Section 5.4, page 5-56.

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> Taken as a whole, the majority of the Group 1 studies imply that **neurodevelopmental impacts due to altered maternal fT4 levels or presence of maternal hypothyroxinemia occur.** In addition, the Group 2 studies (along with several Group 1 studies) also demonstrate adverse impact of maternal hypothyroxinemia on neurodevelopmental outcomes of the offspring. **Overall, the results of this literature review lend support to the concept that maternal fT4, especially in the hypothyroxinemic range, is critical to the offspring's proper neurodevelopment**. Across different age ranges and neurodevelopment indices, **the impact of altered fT4 is seen even with small incremental changes in fT4 (and in populations with fT4 across the "normal" range)**.[7] [Emphasis added]

EPA scientists developed two approaches to developing a reference dose.

- Quantified relationship between perchlorate exposure and maternal fT4 levels in early pregnancy and neurodevelopmental outcomes in children; and
- Estimated amount of perchlorate needed to increase the proportion of low-iodine individuals that will fall below a hypothetical hypothyroxinemic cut point by a define percentage.

Quantified relationship between perchlorate exposure and maternal fT4 levels in early pregnancy and neurodevelopmental outcomes in children.

EPA scientists characterized the relationship between perchlorate exposure and fT4 levels in mothers with low dietary iodine intake and how that exposure changes neurodevelopmental outcomes. Of the 15 studies in Group 1, EPA scientists identified five studies and four neurodevelopmental endpoints that were quantitatively connected to changes in fT4 levels in the first trimester for pregnant women with iodine intake of less than 75 micrograms per day (μg/day). The four endpoints were:

- **Psychomotor Development Index (PDI):** Assessment of fine and gross motor skills such as body control, coordination, and manipulation. It is the other main indices in BSID.
- **Mental Development Index (MDI):** Assessment of cognitive and language development using items related to sensory perception, knowledge, memory, problem solving, and early language. It is one of two main indices for assessing neurodevelopment in children in the Bayley Scales of Infant Development (BSID).
- **Standard Deviation of Reaction Time:** Assessment using the Amsterdam Neuropsychological Test computerized assessment program.
- **Intelligence Quotient (IQ).**

EPA scientists calculated the dose of perchlorate needed to result in a unit change in each of these neurodevelopmental endpoints. They predicted that:

- **PDI:** A dose of 1.7 micrograms of perchlorate per kilogram of body weight per day (μg/kg/day) was needed to decrease the index by one point using data from week 12 of pregnancy;
- **MDI:** A perchlorate dose of 2.2 μg/kg/day was needed to decrease the index by one point using data from week 12 of pregnancy;

[7] EPA Draft Report, Section 5.5, page 5-61.

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- **Reaction Time:** A dose of 3.0 µg/kg/day was associated with a one standard deviation decrease in reaction time using data from week 13 of pregnancy;
- **IQ:** Doses from 6.5 to 45 µg/kg/day were associated with a one point drop in IQ based on two studies with data from gestation week 16 and 13.[8]

Based on this method, the most sensitive endpoint appears to be PDI with IQ being the least sensitive one. It is worth noting that the estimates are based on a limited number of endpoints and health effects. In Section 8 of the report, EPA noted that there are additional potential adverse health effects that were not captured in the analysis to inform the derivation of a perchlorate MCLG.

Estimated amount of perchlorate needed to increase the proportion of low-iodine individuals that will fall below a hypothetical hypothyroxinemic cut point by a define percentage.

Recognizing the risks to a child's neurodevelopment from hypothyroxinemia, EPA scientists evaluated how much perchlorate exposure is needed to shift the proportion of the population that will fall below a hypothetical hypothyroxinemic cut point by 1% or 5%. In other words, how many thousands pregnant women will become hypothyroxinemic in the presence of perchlorate. They acknowledged that:

> This approach does not directly connect the BBDR output to neurodevelopment. However, for pregnant mothers in early pregnancy, this shift could be related to avoiding an increase in the offspring population's risk of adverse neurodevelopmental impacts given the preponderance of evidence located in EPA's literature review that finds an association between hypothyroxinemia and adverse neurodevelopmental outcomes . . .[9]

EPA's scientists defined hypothyroxinemia as the 10th percentile of fT4 of median-iodine intake population of 170 µg/day. The estimated fT4 values at the 10th percentile of a normal iodine intake population corresponded to about 50th percentile of a low-iodine intake population. In other words, approximately 50% of pregnant women with iodine intake less than 75 µg/day would already be hypothyroxinemic.

They predicted that a dose of:

- 0.3-0.4 µg perchlorate/kg/day is associated with a 1% increase in pregnant women with hypothyroxinemia; and
- 2.1-2.2 µg perchorate/kg/day is associated with a 5% increase in pregnant women with hypothyroxinemia.[10]

While these percentages appear small, they represent a significant number of potentially affected children since neurodevelopmental harm is likely irreversible. EPA did not estimate the number of pregnant women or children potentially affected. We did. Based on four million children born

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[8] EPA Draft Report, Section 9, Table 39.
[9] EPA Draft Report, Section 7, page 7-1.
[10] EPA Draft Report, Section 7.1, Table 35 and Section 9, Table 40.

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in the US each year,[11] an estimated 400,000 were born to women with hypothyroxinemia (10th percentile). A 1% shift in the population of women with hypothyroxinemia associated with perchlorate exposure would correspond to an increase of 4,000 impacted children; if there is a 5% shift, the number of children born to hypothyroxinemic mothers would increase to 20,000 impacted children. EPA also considered other percentiles to define hypothyroxinemia and came up with similar perchlorate doses of concern.

Exposure to additional goitrogenic chemicals should be considered.
We understand that EPA's analysis concerns perchlorate exposures. However, as clearly noted in its report, pregnant women are likely exposed to additional chemicals negatively affecting the thyroid gland's function. EPA stated that "[w]hile the BBDR model does not explicitly consider other goitrogens (e.g., thiocyanate, nitrate), simulating results for a mother with low iodine intake and low baseline fT4 may help to address the sensitivity of individuals with high exposures to other goitrogens."[12] We encourage the agency, and its partners at FDA, to continue improving the BBDR model to make it compatible with iodine levels below < 75μg/day to better represent these other exposures that affect the thyroid. Approximately 16% of American women have an iodine intake of 50 μg/day.[13] Until those refinements are made, EPA needs recognize the uncertainty through safety factors.

Safety factors are needed.
EPA clearly recognized the variability in fT4 as an important uncertainty factor in estimating perchlorate exposure associated with low fT4. Specifically, it stated that "…different populations vary widely in their distribution of fT4 levels;" there also are "intra-individual variance in fT4."

These intraspecies and intra-individual variation could be based on physiological fluctuations or due to the presence of other goitrogenic chemicals affecting the thyroid function. For these reasons, we recommend EPA apply at a minimum a safety factor of 10 to the most sensitive endpoints. For the first approach, EPA should use PDI as the most sensitive endpoint to provide a reference dose that would be 0.17 μg/kg/day. For second approach, the reference dose would be the 0.21 μg/kg/day to protect all but an estimated 20,000 affected children and 0.03 μg/kg/day to protect all but an estimated 4,000 affected children.

General observations on the process.
EPA scientists have risen to the challenge presented by the SAB, the previous review panel, and the public comments. They have conducted a rigorous analysis of the science and presented its findings in a coherent and clear manner. Having watched this process over the years, we wanted to take the opportunity to provide some general observations:

1. **EPA's scientists provide an essential service:** Academic researchers laid a solid foundation for the analysis. Without their work, typically funded by government grants, we would not have the evidence necessary to recognize the harm from perchlorate at the levels under consideration. But it took the independent scientists at EPA, building on a

[11] Centers for Disease Control and Prevention, National Vital Statistics System, Birth Data accessed on November 4, 201 at https://www.cdc.gov/nchs/nvss/births.htm.
[12] EPA Draft Report, Section 3.5, page 3-15.
[13] Caldwell KL, et al. (2013) Iodine Status in Pregnant Women in the National Children's Study and in U.S. Women (15-44 years), National Health and Nutrition Examination Survey 2005-2010. Thyroid 23:927-937

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model developed by FDA, to provide the objective rigorous review of the evidence and adapt the model.

2. **Peer-review process works:** The agency rose to the challenge of two previous peer-review panels, one established by EPA's SAB and the other by EPA's Office of Water. The panels operated in a transparent process and provided independent and objective review of the analysis by EPA. We anticipate that this third and final panel will do the same. The integrity of the process depends on credibility of the experts on the panel. Screening out these experts because they receive government funding as EPA is now doing[14] is irresponsible and unlawful. It undermines the quality of the review and the credibility of the process.
3. **Incremental changes in free T4 (fT4) are fundamental:** Critical neurodevelopmental adverse effects could be missed by measuring full range maternal fT4. Windows of susceptibility are common in all organs during development. Hormonal control of brain development is no exception. Therefore, adverse neurodevelopmental outcomes will vary based on the time and duration of decreases in fT4 levels. We appreciate seeing the agency building a model based on this fundamental principle of developmental biology.

For questions, please contact us at tneltner@edf.org or 202-572-3263 for Tom Neltner, eolson@nrdc.org for Erik Olson, or drmvma@gmail.com for Maricel Maffini.

Sincerely,

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[14] EPA Administrator, Strengthening and Improving Membership on EPA Federal Advisory Committees, October 31, 2017. See https://www.epa.gov/faca/strengthening-and-improving-membership-epa-federal-advisory-committees.

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Environmental Working Group

November 20, 2017

Samuel Hernandez
U.S. EPA, Office of Ground Water and Drinking Water
Standards and Risk Management Division, (Mail Code 4607M), 1200
Pennsylvania Avenue NW
Washington, DC 20460;

RE: Comments on EPA's Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water at Docket No. EPA-HQ-OW-2016-0438

Dear Mr. Hernandez:

The Environmental Working Group, a nonprofit research and advocacy organization based in Washington, DC, submits comments on the Environmental Protection Agency's draft report Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal (MCLG) for Perchlorate in Drinking Water.

Perchlorate exposure is of utmost concern for children's health because as of 2005-2010, the latest period for which data are available, more than half of all pregnancies in the U.S. were recorded for women with iodine intake below the WHO recommendation of 250 micrograms per day.[1] The EPA draft proposal represents a true step forward for protecting the health of American children from this toxic chemical that contaminates food and drinking water. EWG also wholeheartedly supports the detailed comments submitted by the Environmental Defense Fund and Natural Resources Defense Council.

In this letter, EWG highlights three main messages:

- The approaches for perchlorate MCLG derivation outlined in the draft report are scientifically sound and should be adopted for the final agency decision.

- The EPA should use a minimum tenfold safety factor when establishing a reference dose for perchlorate to account for human variability in thyroid vulnerability, and the prevalence of other goitrogens in water and food.

- The EPA's analysis conclusively demonstrates that the existing Reference Dose (RfD) of 0.7 ug/kg-day is not protective of public health and needs to be lowered.

Details and rationale for EWG's recommendations are provided below.

1. EWG supports the modeling and approaches outlined in the draft report.

EWG commends the Agency's modeling of perchlorate effects on the maternal thyroid gland in women with low iodine intake during pregnancy. EWG finds that the EPA has thoroughly reviewed the literature for both perchlorate effects on thyroid homeostasis, and synthesized a sizable body of literature linking thyroid perturbations during pregnancy and early life with altered brain development and motor control in young children. In our assessment, the EPA's method is rigorous, transparent, and appropriately evaluates perchlorate risks for the most vulnerable population and time periods, specifically with the additional focus on women with hypothyroxinemia during the first trimester of pregnancy.

2. EPA must use appropriate safety factors when determining acceptable perchlorate exposure.

While EPA's modeling is high quality and appropriately based on studies of perchlorate's effects on human pregnancies, important uncertainties remain. EWG is concerned that the draft EPA model may not capture the full variability of maternal response to thyroid perturbation, and does not account for women with pre-existing thyroid disease who may be more affected by perchlorate exposure.

EWG also notes that perchlorate intake does not occur in isolation. During pregnancy, women and the developing fetus are also exposed to other chemicals harmful to the thyroid. The EPA model did not explicitly account for the effects of concurrent exposures to certain goitrogens, such as thiocyanate and nitrate.

The EPA draft proposal has also neglected to consider chlorate, another goitrogen commonly detected in food and drinking water. Chlorate forms when drinking water is disinfected with hypochlorite bleach. Like perchlorate, chlorate is also formed when bleach degrades due to inadequate management conditions. If bleach is then used to disinfect food handling equipment and produce, both perchlorate and chlorate could contaminate food simultaneously, increasing the risk of harm to the thyroid. The European Food Safety Authority's 2015 assessment of chlorate bases its assessment of chronic exposure on the risk of iodine uptake inhibition, the same toxicity pathway that is affected by perchlorate.[2]

EWG urges the EPA to employ a minimum tenfold safety factor in the development of its reference dose for perchlorate to account for the outstanding uncertainties and to protect against the significant, lasting effects perchlorate exposure can have on children's brain and motor development.

3. Existing Reference Dose of 0.7 ug/kg-day is not protective of public health and needs to be lowered.

The reference dose for perchlorate exposure currently in effect was established by the EPA in 2005 and was based on a No Observed Effect Level (NOEL) reported in a study of thyroid function for healthy adult volunteers. The latest research conclusively demonstrates that data from non-pregnant adults, even with the use of additional uncertainty factors, does not adequately predict risks of thyroid hormone disruption during the sensitive life stages of gestation and childhood. Thus, the Agency's proposal to model effects of perchlorate exposures during pregnancy represents a true advance for children's health protection.

The EPA's draft released for comment in September 2017 presented two methods to evaluate adverse effects of perchlorate exposure. Both methods produced similar outcomes, demonstrating the overall robustness of the EPA proposal.

The EPA's first method assessed the impact of perchlorate on the circulating levels of free thyroxine, a thyroid hormone also called free T4 (fT4), in mothers with low dietary iodine. It identified four health endpoints that can be quantitatively correlated with maternal fT4 levels in pregnant women with low iodine intake. EWG recommends that EPA base its reference dose on the most sensitive outcomes associated with perchlorate exposure, a change in the infant Psychomotor Development Index. Exposure to 1.7 micrograms of perchlorate per kilogram of bodyweight per day during week 12 of pregnancy is expected to cause a one-point decrease in the Psychomotor Development Index in childhood. The reference dose and the future MCLG for perchlorate must protect against this type and degree of change in psychomotor development.

The EPA used a second method to determine the amount of perchlorate exposure that would shift additional American pregnancies towards the condition of hypothyroxinemia. The EPA defined the hypothyroxinemia cutpoint as the lower 10th percentile level of fT4 in a population with median iodine intake. The EPA's analysis points out that hypothyroxinemia during pregnancy is associated with poorer neurodevelopment in infants, including lower non-verbal intelligence, slower reaction times, non-verbal cognitive delays, as well as profound outcomes with life-long consequences such as schizophrenia, attention deficit hyperactivity disorder and autism.

The EPA draft report calculated that a dose of 0.3 - 0.4 ug/kg of perchlorate per day will cause a 1 percent increase in the number of pregnant women with clinically defined hypothyroxinemia, and a dose of 2.1 - 2.2 ug/kg per day will cause a 5 percent increase. The analysis jointly developed by the Environmental Defense Fund and Natural Resources Defense Council indicates this would impact 4,000 and 20,000 U.S. pregnancies, respectively.

The modeling EPA presented clearly indicates that the current reference dose for perchlorate is not protective of public health and must be lowered. Using any of the points of departure identified above, and applying a minimum tenfold safety factor will protect many thousands of pregnancies in the United States today and the health of American children.

In conclusion, EWG finds that the EPA scientists have successfully addressed the central question raised by EPA's Science Advisory Board in 2013 and the agency's peer review panel, regarding the relationship between perchlorate exposure in the first trimester of pregnancy and a child's neurodevelopmental outcomes when the mother has insufficient iodine intake.

Submitted on behalf of the Environmental Working Group,

Sonya Lunder, MPH, Senior Analyst

Olga Naidenko, Ph.D., Senior Science Advisor

References:

[1] KL Caldwell, et al. Iodine status in pregnant women in the National Children's Study and in U.S. women (15-44 years), National Health and Nutrition Examination Survey 2005-2010. Thyroid, 2013. 23(8):927-37.

[2] EFSA. 2015. Scientific Opinion: Risks for public health related to the presence of chlorate in food. European Food Safety Authority. EFSA Journal 13(6):4135.

NASA

National Aeronautics and
Space Administration

Headquarters
Washington, DC 20546-0001

November 20, 2017

Reply to Attn of: Environmental Management Division

U.S. Environmental Protection Agency
EPA Docket Center
Attention: EPA-HQ-OW-2016-0438
Mail Code 28221T
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Request for Public Comments To Be Sent to EPA on Peer Review Materials To Inform the Safe Drinking Water Act Decision Making on Perchlorate [82 FR 43354; September 15, 2017]

The National Aeronautics and Space Administration (NASA) appreciates the opportunity to review and comment on the "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (Volumes 1-3)." NASA reviewed the draft Report and is providing general and specific comments, including observations on EPA's Draft Charge Questions under separate review, to promote consistency and clarity for EPA's proposed submission for Peer Review.

EPA's Draft Report, supporting Draft Charge Questions, and Interim List of Peer Reviewers form the technical basis of EPA's efforts to obtain formal, independent peer review to guide future efforts in the establishment of a Maximum Contaminant Limit (MCL) for Perchlorate in Drinking Water. NASA provides its comments (attached) to support sound, defensible, science-based decision making. We understand that the purpose of this Report is to provide modeling capability that serves as the foundation of future regulatory actions. NASA strongly encourages EPA to focus this Report and its supporting documents to validate and strengthen critical aspects of the proposed model. Our comments address issues within the Draft Report and include suggestions for direction to the Peer Review Committee to address outstanding issues or concerns with the current draft Report.

NASA acknowledges and appreciates that EPA addressed numerous technical comments provided in an earlier public review of the proposed model and during peer review in January 2017. Our overarching comments and specific issues related to the current report are provided in Attachment A.

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NASA looks forward to continued cooperation with EPA to ensure safe and successful execution of our mission. If you have any questions concerning these comments, please contact Dr. Linda Wennerberg at 202-358-4558.

Sincerely,

Mike A. McNeill
Deputy Director, Environmental Management Division

Enclosures
cc:

Environmental Management Division
- Dr. Wennerberg

Marshall Space Flight Center
- Ms. Grafton

NASA General/Systemic Comments on the Draft Report:

- EPA's decision to split public comment and review of the proposed Draft Report from the Draft Charge Questions and Interim List of Peer Reviewers is both troubling and confusing. The Agency's approach fragmented traditional public review and undercut the established method to target charge questions to consider areas of scientific disagreement or controversy and ensure appropriate expertise on the peer review panel. NASA found this artificial separation of key aspects of independent peer review concerning and requests that EPA integrate emerging public comments into the final charge questions for the peer review panel. EPA also needs to review the Peer Review Committee membership to ensure appropriate expertise upon the comments received during this public comment period. NASA's comments identify key issues for peer review consideration.
- NASA strongly encourages EPA to consider the in-depth and substantial technical input provided by the Department of Defense (DoD) and the Food and Drug Administration (FDA), due to their unique experience and expertise in the development of the proposed model and evaluation of impacts on human neurodevelopment. NASA concurs with this well-supported technical input provided in comments to the docket by experts in these and other Federal Agencies. We support this public review to strengthen EPA's modeling efforts to develop a scientifically defensible MCL for perchlorate.
- The input from experts within DoD and FDA is especially critical as EPA has not provided an independent validation of the model or its underlying assumptions. The lack of model validation and transparent understanding of the intricacies of this proposed model, such as its underlying assumptions, handicap ready public review. The complexity of the Draft Report and its lack of transparency compound difficulties in rapid and informed public review and comment. Again, EPA is encouraged to consider expert input on the model from its fellow Federal Departments and Agencies, as well as the public.
- The lack of targeted behavioral or social science expertise within EPA or on the proposed Interim List of Peer Reviewers, including population statisticians and clinical psychologists, raises significant questions due to the stated Draft Report focus on neurodevelopmental impacts. Neurodevelopmental studies vary significantly by design, methodology, definition, and analysis. Such studies often generate controversy and disagreement, especially when considering very low levels of impact, such as the change in one IQ point. EPA provides little clarity on the choice of individual neurodevelopmental studies or their applicability for specific perchlorate exposures. EPA does not provide substantiation that supports treating a diverse set of outcomes as related endpoints. NASA strongly encourages EPA to include clear charge questions and also appropriate expertise to ensure a more defensible peer review and model formulation.
- EPA intends to use this proposed model to estimate the impacts of perchlorate exposure on identified sensitive subpopulations and subsequent neurodevelopmental impacts. This dose response approach relies heavily on

literature targeting a controversial clinical pre-condition (not a disease state) of hypothyroxinemia in women in early stages of pregnancy. The choice to focus on hypothyroxinemia, a clinical designation that is subject to interpretation, fuels concerns as EPA applies conservative assumptions and uncertainty considerations in the interpretation of the model and literature results. This broad area of concern necessitates the need for clear direction to the peer reviewers to evaluate EPA's proposed approach.

- NASA notes that the EPA Science Advisory Board (SAB) directed EPA to consider this conservative state in the pregnant woman and focus on the more sensitive first trimester of pregnancy after the first January 2017 peer review. The SAB also stated that EPA should use a Biologically Based Dose-Response (BBDR) model approach (referred to as the proposed model). EPA needs to ask the proposed peer review to review and comment on whether EPA adequately addressed the January 2017 peer review direction and if the proposed Draft Report and BBDR model are appropriate and scientifically defensible. In review of this Draft Report, NASA finds EPA does not adequately evaluate whether previous SAB and January 2017 peer review comments have been addressed. A charge question directing the Peer Review Committee is most appropriate.
- The bulk of the Draft Report focuses on a literature review, starting with 55 studies and the detailing of the final 5 studies selected to support the model. EPA devotes significant attention to detailing the studies in the literature review but limited discussion on how these studies inform the derivation of an MCLG or the underlying assumptions and determinations by EPA. EPA offers scant clarification of the uncertainties and clear relationships between the chosen studies and the proposed model. The lack of specificity in this crucial basis of the Draft Report should be considered more in-depth by the peer reviewers.
- EPA appeared to select only studies with positive impacts and not to use studies that did not demonstrate a direct relationship.
- EPA acknowledged that it relied on EPA's own digitization of data from figures in key studies and lacked direct evaluation of the supporting data, potentially impacting on the analysis of uncertainty and other factors.
- The process EPA lays out to actually use those 5 studies for predictions from the proposed BBDR model, the derivation of the distribution of fT4 (to correlate hormone levels and potential impacts to a developing fetus), and then the relationship for fT4 and specific neurodevelopmental impacts again gets limited discussion or explanation in the Draft Report. The reader is left with a very disjointed understanding, which reads that one set of events happen, then other events happen, and then EPA is able to make definitive statements on how doses of perchlorate relate to potential neurodevelopmental impacts. EPA does not adequately delineate how the studies inform the model or define how the progression of exposure to a defined impact occurs. Confounders, such as the presence of other goitergens or smoking in the pregnant woman, are simply ignored. The overall progression of exposure, dose, and result are not clearly

defined in the Draft Report and should be subject to focused peer review evaluation and direction.

- EPA is strongly encouraged to review and correct assertions and language throughout the Draft Report that is incorrect or inaccurate. Draft Report language contains errors and contradictions that confuse and mislead the reader. Examples include false attribution to the National Academy of Sciences (NAS) report (2005) that "main source of perchlorate is rocket fuel, by both the defense and aerospace industries". In fact, the NAS noted that assessment from a draft EPA report but declined to support EPA's draft language. In Chapter 8, "Other Health Effects Potentially Associated with Perchlorate", EPA repeatedly identifies potential health effects but then later states that there is no proof that perchlorate actually causes these health effects. NASA requests EPA remove inaccurate or misleading statements to minimize confusion for the peer reviewers and the public. Chapter 8, in particular, offers unsupported statements that do nothing to support sound model development in the Draft Report and simply offer confusing, inflammatory statements. NASA requests EPA remove Chapter 8, as it offers no support for the model development or derivation of an MCL, or direct the Peer Review Committee to not review and comment on this Chapter.
- In addition to the need for EPA to review and reduce confusing or inaccurate statements throughout the document, sizable amounts of the Draft Report discuss alternative studies or efforts that do not support the SAB direction for the BBDR model development. Extensive discussion of alternative approaches, such as those authored by Steinmaus, in the Appendices B and C, serve to confuse the reader and distract from the stated purpose of the Draft Report while offering little substance to implement the SAB's direction to EPA. NASA concurs with EPA's decision not to address any of these distracting alternatives in the initial draft charge questions; however, we also request EPA either edit the Draft Report to clarify the focus specifically on the SAB direction and the development of a defensible BBDR model or to direct the peer reviewers to not review or consider these alternative approaches. Inclusion of such alternatives does little to support model development and offers a significant distraction from the stated SAB direction.
- The overall thrust of the proposed BBDR model is the estimation of the dose and impacts from perchlorate exposure on the identified sensitive subpopulation. A very limited set of studies directly addressed dosage of perchlorate and EPA provides little clear discussion of how dose-response relationships clearly link perchlorate to the targeted neurodevelopmental effects. EPA's chosen studies point to the potential for alterations in thyroid hormone levels to lead to impacts in human neurodevelopment. Again, the Draft Report focuses extensively on a literature review but provides limited discussion of key assumptions, assessment of uncertainties, and the clear mechanisms in the proposed model to estimate perchlorate dose-response impacts on neurodevelopment in humans.
- EPA is silent on declining levels of perchlorate in water and other environmental media. The potential for exposure, especially at low doses, raises the question if

this proposed model and EPA's assumptions reflect that actual state of low levels of perchlorate in the environment.

NASA Specific Comments:

- Again, NASA concurs with technical comments and issues identified by DoD and FDA with the proposed model and the utilization of studies on neurodevelopmental impacts. EPA is encouraged to consider the expertise and input from Federal Agencies.
- Page 1-3: EPA discusses contradictory studies that directly relate to perchlorate exposure but does not provide clear direction on how these contradictory studies support the proposed model. NASA requests that EPA provide clearer direction to the Peer Review Committee to evaluate the applicability of these studies and others to support model development.
- Page 1-4: EPA discusses efforts to establish a Health Reference Level (HRL) but does not include any discussion of attributes from the NAS Report (2005) that formed the basis of the IRIS value for perchlorate. EPA is encouraged to provide a summary of the NAS determination for consideration and completeness,
- Pages 2-6 to 2-8, 3-15: The issue of other goitergens, such as isocyanate, and exposure to environmental contaminants, such as endocrine disruptors, or behaviors, such as smoking, serve as potential confounders to the production of T4 by the thyroid is identified. However, EPA does not provide resolution on the issue of confounding. Again, EPA is encouraged to request peer review direction on this matter to support a more robust Mode of Action approach, building on previous efforts by NAS.
- Pages 3-5 to 3-9, 3-16 to 3-18, 4-6: EPA provides a summary of key model parameters but does not also provide independent model validation or substantive explanation of key assumptions or fundamental uncertainties. Validation of this model and the delineation of assumptions are critical to model review. EPA needs to directly address these issues in charge questions and through the sharing of the model to the Peer Review Committee.
- Pages 5-1 to 5-17: Peer review needs to expressly review EPA's approach to implement the SAB direction to "identify literature and conduct analysis to support the model outputs for the downstream effects". Key assumptions on the process to assign compatibility of studies for inclusion, limitation of the review, and selection of downstream effects form the basis of EPA's analysis. EPA's approach consolidates a range of assumptions, study choices, and a diverse set of outcomes (such as autism, ADHD, and neurodevelopmental measures) not readily linked.
- Pages 5-8 to 5-61, Appendix G: Focused peer review is needed to evaluate EPA's methodology, grouping, and interpretation of key studies, especially as EPA intentionally targeted studies that identified correlation with a range of neurodevelopmental outcomes. NASA identified this concern in our General/Systemic Comments, as well as the need for specific expertise in the

assessment of development, execution, and interpretation of neurodevelopmental studies.

- Pages 6-5 to 6-6: EPA assumes an inherently more conservative stance by focusing its analysis on the lower range of the distribution. This approach and other conservative assumptions raise the potential for skewing the choice and application of study results in the derivation of the MCLG. NASA noted this concern under the General/Systemic Comments and requested peer review of EPA's methodology.
- Pages 6-14 to 6-17: EPA provides limited discussion of key assumptions and methodologies to identify and address uncertainty to EPA's approach and the actual model development. This issue, previously noted under General/Systemic Comments, requires directed peer review on key aspects of definition of population, endpoints, estimated Iodine intake, and the process of maternal fT4 measurement. These issues are the foundation of assumptions driving the proposed model and EPA's limited discussion highlights the need for in-depth peer review and guidance.
- Page 6-19: EPA provides a limited explanation of its methodology to address significant confounding and interacting variables, and other screening factors in study selection. Again, NASA requests that EPA's methodology be evaluated in the peer review.
- Pages 7-1 to 7-2: The diverse set of targeted neurodevelopmental endpoints and EPA's methodology to connect shifts in fT4 to specific neurodevelopmental indicators merits peer review and assurances to include applicable technical expertise in the evaluation of such studies. Again, EPA provides limited discussion of uncertainties, the impact of other goitergens, and Agency assumptions on these critical relationships.
- Page 7-4 to 7-6: EPA addresses broadly, and with limited discussion, significant uncertainties on the hypothyroxinemia condition and its implications for early pregnancy mothers. EPA's discussion is confusing and truncated. Peer review must evaluate these critical EPA assumptions and decisions impacting on model development.
- Pages 8-1 to 8-3: EPA is strongly encouraged to remove this confusing Chapter to minimize its conflicting discussion and minimize confusion. This issue, previously identified in General/Systemic Comment, highlights the need for EPA to address the direction from the SAB for model development and assessment.
- Pages 9-1 to 9-2: EPA's summary of conclusions into two tables would benefit from clear and more detailed description, outlining the Agency's conclusions that form the basis of informing of an MCLG.

Perchlorate Study Group

(including comments prepared by Intetox, Inc.)

PSG

PERCHLORATE STUDY GROUP

A coalition of aerospace, defense, chemical and allied industries

November 20, 2017

Michael H. Shapiro
Acting Assistant Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

RE: FEDERAL REGISTER NOTICE [EPA–HQ–OW–2016–0438; FRL–9967–69–OW (SEPTEMBER 15, 2017)]

Dear Acting Assistant Administrator Shapiro:

The Perchlorate Study Group (PSG) has worked with the U.S. Environmental Protection Agency (EPA) for 20 years studying potential health effects from perchlorate exposure. From funding research to providing scientific comments and meeting with the Agency, we have consistently supported using the best available science to determine whether perchlorate should be regulated under the Safe Drinking Water Act. It is in this context that we offer the attached comments on EPA's *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (Draft Report).*

The PSG supports EPA's decision to use a Biologically-Based Dose Response (BBDR) model to identify potential impacts from perchlorate exposure at relevant life stages. The PSG concludes that this approach, when developed with all critical clinical thyroid parameters and validated in a transparent manner, constitutes the best available science for addressing areas of uncertainty for the pregnant woman and her fetus. This approach has been endorsed by the National Research Council (NRC)[1] perchlorate panel and the 2013 EPA Science Advisory Board (SAB) perchlorate panel. *Moreover, when the most sensitive population is protected, all other populations are protected.*

The BBDR model has been improved significantly since the first peer review earlier this year. Additional work would improve the model even further to achieve our shared goal of ensuring that any perchlorate regulatory decision is based on the best available science. Specifically, various model inputs are overly conservative and, as a result, the model predicts potential impacts from perchlorate exposure that are extremely unlikely. While using conservative inputs may be best practice for conducting environmental risk assessments, it is not best practice for model development. Model inputs should be as realistic as possible to produce results that are as realistic as possible.

[1] National Research Council, *Health Effects of Perchlorate Ingestion*, Jan. 2005.

Even with these overly conservative inputs, however, the model buttresses the conclusion that no adverse health effects occur from perchlorate exposure at levels found in the environment, which are generally less than 4 ppb. In clinical studies, no *measurable* effects occur with perchlorate exposures of 245 ppb or less.[2]

We also see clear indications of bias in the Draft Report's literature search relative to identification of studies investigating potential neurodevelopment impacts from perchlorate exposure. Notably, EPA selected only five studies that found an association ("positive studies"). At the same time, EPA ignored seven studies that reported no association. While this weight of evidence should not be overlooked in EPA's analysis, even this biased approach leads to the same conclusion: *EPA's assessment does not demonstrate adverse health effects atexposure levels greater than the EPA reference dose (RfD).*[3] This conclusion is also supported by a robust set of animal studies that consistently demonstrate no significant changes in neurodevelopment at perchlorate concentrations much higher than environmental levels.

The BBDR model appears to be fit-for-purpose in supporting a determination that perchlorate does not cause adverse health effects at environmentally relevant concentrations. However, given the shortcomings noted here and in the attached technical comments, the model is not fit-for-purpose in deriving a numerical Maximum Contaminant Level Goal (MCLG). Further development and refinement of the model would be necessary to achieve this goal. This latter issue is largely moot, however, because the overwhelming weight of evidence from six decades of perchlorate research strongly supports the conclusion that there are no adverse neurodevelopmental effects from exposure to perchlorate at environmental levels.

In addition to these overarching issues, we recommend EPA address the following concerns and submit them to the second peer review panelists for their consideration:

- EPA should follow the NAS recommendations in its 2011 and 2014 reports on the IRIS program for conducting systematic review, evidence evaluation, and evidence integration. Other critical studies are available that the Agency should include as part of its scientific review over and above those considered by EPA in the Draft Report.

- EPA's decision to focus on hypothyroxinemia as a critical endpoint is not supported by the best available science or by public health professionals in the field. Hypothyroxinemia is merely a research construct; it is *not* a recognized medical condition treated by clinicians. The NAS 2005 perchlorate panel identified the pregnant woman with hypothyroidism as the most sensitive population based on the best available science. Accordingly, EPA should abandon further consideration of the hypothyroxinemia endpoint.

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[2] The lowest reported No Observable Effect Level for a non-adverse effect was reported in Greer et al. (2002) as 7 µg/kg-d. This is equivalent to 245 ppb in water assuming a 70-kg adult drinking 2 L/d.
[3] The RfD is equivalent to 24.5 ppb in drinking water assuming a 70-kg adult drinking 2 L/d. The RfD includes an uncertainty factor to account for all sensitive populations.

- The PSG concurs with EPA's decision not to include the approach presented in Appendix C for further consideration by the peer review panel or by the agency. The use of a single epidemiological study, rather than the BBDR model, is not scientifically valid for purposes of making a perchlorate regulatory determination, much less for derivation of an MCLG.

- As noted in the letter from Intertox on October 6, 2017, the PSG also urges EPA and Versar, Inc. to ensure that the second peer review panel includes all relevant areas of scientific expertise necessary for conducting a comprehensive review of EPA's proposed MCLG approaches presented in the Draft Report.

- The PSG disagrees with inclusion of the information contained in Chapter 8 of the Draft Report. With the exception of hypothyroidism, which we agree is a potential (although undocumented) adverse effect of perchlorate exposure at sufficiently high doses, the other hypothesized endpoints have not been reported to be caused by perchlorate exposure.

The PSG appreciates EPA's consideration of our comments, and we look forward to a rigorous second peer review process and thoughtful analysis of the above and attached issues.

Sincerely,

Jason Leuck

Jason Leuck
Chair, Perchlorate Study Group

INTERTOX

COMMENTS ON
DRAFT REPORT: PROPOSED APPROACHES TO INFORM THE DERIVATION OF A MAXIMUM CONTAMINANT LEVEL GOAL FOR PERCHLORATE IN DRINKING WATER

FINAL

Prepared for:

PERCHLORATE STUDY GROUP

November 20, 2017

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EXECUTIVE SUMMARY

The US Environmental Protection Agency (EPA) is considering approaches to develop a perchlorate Maximum Contaminant Level Goal (MCLG). On September 15, 2017, EPA published a notice announcing the release of materials for public comment in the Federal Register (EPA–HQ–OW–2016–0439; FRL–9967–70–OW). The Agency has proposed a scientific review that requires the expertise of at least three diverse scientific disciplines. These are Biologically-Based Dose Response (BBDR) modeling, thyroid endocrinology, and neurodevelopmental testing. Aspects of these three disciplines have been integrated to develop two approaches to inform MCLG development. Although the purpose is unclear, an exercise is presented in Appendix C that might also be construed as an approach. We have reviewed these approaches and the underlying science and present our comments to EPA and the Peer Review Panel in this document.

BBDR Modeling

The BBDR model was improved following the first Peer Review. We commend the Agency for exploring the use of BBDR models to understand aspects of toxicology where data are not available. The current Reference Dose (RfD) for perchlorate is based on a *non-adverse* effect with an uncertainty factor (UF) to account for the most sensitive population, pregnant women. We recognize the utility of using EPA's model to inform on an *adverse* effect in the most sensitive population, thus obviating the need for any UF. However, the documentation of the model continues to be incomplete. For example, predicting the effects of iodine deficiency in the absence of perchlorate exposure is a fundamental task for this model. The ability of the model to accurately predict epidemiological data on iodine deficiency in pregnancy has not been demonstrated. Additionally, decisions were made to increase the conservatism of the model (e.g., using a weak TSH responder as the model subject). Thus, while the model does not provide outputs for an average pregnant woman, these outputs are later considered the mean of the distribution.

A scientifically-sound and transparent model can help inform the MCLG process. We recommend the Agency improve the transparency, present validation of the model, and provide a clear understanding of the model limitations.

Hypothyroxinemia

The output of the model is used to define a population of pregnant women as hypothyroxinemic, which is not scientifically defensible. The 2012 Science Advisory Board (SAB) recommended that EPA focus on "thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure." There were no thyroid endocrinology clinicians on the SAB panel that suggested using hypothyroxinemia as an adverse endpoint. Based on the SAB's report, EPA has essentially adopted a new mechanism of action (MOA) for perchlorate despite widespread acceptance of the MOA described by the NRC (2005), which identifies hypothyroidism as the first adverse effect due to perchlorate. There are no studies reporting that perchlorate causes isolated hypothyroxinemia in pregnancy, which is EPA's proposed MOA. In fact, studies of first trimester pregnant women repeatedly report no association between perchlorate and thyroid hormone levels. Notably, just prior the first Peer Review meeting, the American Thyroid Association (ATA) published its authoritative guidelines on care during pregnancy and recommended no treatment of hypothyroxinemia in pregnancy.

We recommend the Agency use hypothyroidism as the adverse effect in the BBDR model.

Neurodevelopmental Testing

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The use of neuropsychological testing for the prediction of neurodevelopmental outcomes based on fT4 is not scientifically defensible. The Agency proposes multiple endpoints that are controversial from a scientific standpoint. Neurodevelopmental tests were developed to identify individuals with clear disability. The Agency has based its assessment on the mathematical relationships represented in five studies that reported effects caused by dramatically different doses of perchlorate. These studies were conducted in populations unlikely to be relevant to US exposures. More importantly, these studies lacked sufficient consideration of confounders, and lack sensitivity and specificity to detect small individual differences. EPA used only studies that reported an association and excluded a larger number of studies that did not. Lastly, EPA did not include discussion of animal studies that reported no impact from perchlorate exposure on a wide variety of neurodevelopmental outcomes.

The literature supporting the association between hypothyroxinemia and adverse neurodevelopmental outcomes is equivocal at best, and lacks the predictive power necessary to form the basis of a regulation. Consistent with the established perchlorate MOA and the weight of scientific evidence, the Agency should consider neurodevelopmental effects as downstream from hypothyroidism.

Conclusion

We have consistently supported the use of a BBDR model that is transparent and scientifically sound. We are pleased that EPA has proceeded along this track and encourage its continued improvement for use in this process. It is clear that the research available on hypothyroxinemia and the association to neurodevelopmental outcomes is not sufficiently robust for use in a predictive manner to provide the basis of a nation-wide drinking water regulation.

It is noteworthy that, despite the conservatism in the BBDR model, it predicts that doses of perchlorate well in excess of environmental levels produce only small changes in fT4. For example, the model predicts that in an iodine deficient 12-week pregnant woman, a small fT4 change from 8.85 pmol/L to 8.27 pmol/L requires a perchlorate dose of 10 μg/kg-d (equivalent to a drinking water concentration of 350 ppb on a daily basis). The current RfD is 0.7 μg/kg-d and drinking water concentrations rarely exceed 4 ppb. Clearly, the model suggests the current RfD is health protective of even the most sensitive populations.

The 2012 SAB urged EPA to consider sensitive life stages, use a model to estimate iodide uptake inhibition, use empirical observations to relate iodide uptake inhibition to thyroid hormone perturbations, and consider specific adverse effects on brain development. EPA has developed a model to consider an effect in the *most* sensitive life stage. By evaluating hypothyroidism, EPA could develop an MCLG that would prevent any adverse neurodevelopmental outcome as this is a recognized downstream effect based on NRC's MOA.

In developing health-based guidelines for the nation's drinking water, EPA has an exceedingly important job and one that must always be based on the best available science. We appreciate the clear effort in the improvement of this model with each iteration and continue to believe in its potential utility in informing the MCLG.

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1.0 INTRODUCTION

In June 2016, the US Environmental Protection Agency (EPA) stated:

> EPA is considering deriving a perchlorate MCLG [Maximum Contaminant Level Goal] by linking BBDR model output to alterations in thyroid hormone status that result in alterations in neurodevelopment. The draft approach for deriving a perchlorate MCLG outlines an assessment of the literature linking alterations in thyroid hormone status to alterations in neurodevelopment. Based on the results of this literature review, the report describes potential approaches to set the MCLG based on the availability of the current literature and the output of the BBDR model, predicting the effects of perchlorate on serum thyroid hormone concentrations in infants exposed via ingestion of formula mixed with contaminated drinking water or breast milk (see 81 FR 10617, March 1, 2016).

On September 15, 2017, EPA published a notice announcing the release of materials for public comment in the Federal Register (EPA–HQ–OW–2016–0439; FRL–9967–70–OW). EPA released the following documents:

- *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (Volume I – Main Report)
- *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (Volume II – Appendix A)
- *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (Volume III – Appendices B-G)
- *Requests for Comments: Interim List of Perchlorate in Drinking Water Expert Peer Reviewers and Draft Peer Review Charge Questions*
- *Revised Perchlorate BBDR Model - Code Information*

Prior to this submission, Intertox commented on the charge questions and the list of peer review candidates to EPA's managing contractor, Versar, Inc. (Provided as Appendices A and B).

EPA has presented three general approaches to an MCLG. Two approaches are detailed in the main document. However, a third option is presented in detail in Appendix C of the EPA report. It is unclear why this approach is presented as an appendix. However, we evaluate it, nevertheless, on the off chance that it is intended to be a serious approach.

In summary, these are the three approaches.

> Approach 1: The Biologically-based Dose Response (BBDR) model is used to estimate maternal free thyroxine (fT4) levels with different intake levels of iodine and perchlorate. A change in fT4 is used to predict neurodevelopmental deficits in offspring based on epidemiological studies.
>
> Approach 2: The BBDR model is used to predict a population shift comparing the number of women who would be considered hypothyroxinemic.
>
> Approach 3 ("Appendix C"): The results of a single epidemiological study are used to predict a relationship between perchlorate and maternal fT4. A change in fT4 is used to predict neurodevelopmental deficits in offspring based on epidemiological studies (only one study is used as a demonstration).

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The Perchlorate Study Group (PSG)[1] requested Intertox to review and provide scientific comments on the documents listed above. We will discuss the common and overarching topics (Section 2.0), the three approaches for use in developing a MCLG (Section 3.0), other issues (Section 4.0), and consideration of other goitrogens with the same mechanism of action (MOA) (Section 5.0).

2.0 OVERARCHING TOPICS

As noted in Section 1, we list the three general approaches are presented by EPA for use in deriving an MCLG. In this section we address commonalities that carry through all approaches. We discuss the scientific merit of: the BBDR model, hypothyroxinemia as an endpoint, the use of neurodevelopmental testing studies to predict changes in outcome with changes in fT4, and consistency with the clinical data.

2.1 EPA's Revised BBDR Model

EPA's first version of the BBDR model was Peer Reviewed in January 2017 with a final Peer Review report released in March of 2017. While the BBDR model has been revised since the previous version, we reviewed the revised BBDR model and find that, as a result of multiple overly-conservative inputs, it over-predicts the health impacts of perchlorate exposure. BBDR and physiologically-based pharmacokinetic (PBPK) models are tools that should accurately predict human physiological events which they are intended to characterize. Unlike a risk assessment, which errs conservatively to be health protective, a model should not contain multiple conservative inputs. These compounded inputs will result in an uncertain amount of conservatism that is unrealistic.

The models should accurately predict relevant and critical clinical parameters, the same ones that thyroid endocrinologists use to diagnose a disease. In the case of the thyroid, the American Thyroid Association (ATA) regularly publishes and updates science-based guidelines on the diagnosis and treatment of disease in pregnancy (ATA, 2017). The model should produce relevant information such that the variables that are commonly used to assess thyroid-related disease are predicted. After the development of a model, the Agency then decides whether the contaminant in question needs to be regulated to protect the public health. If necessary, it can apply—in a transparent manner—"safety factors" or adjustments to the output.

We concurred with the Peer Review panel that several necessary aspects were missing from the BBDR model. That is: 1) TSH feedback; 2) focus on the first trimester pregnant woman; and 3) include other goitrogens in the assessment. We are pleased to see that the former two have been integrated into the revised model.

In addition, we previously implored EPA to increase transparency in the studies used to define model inputs, the effect of changes to the model, and what steps were taken after the sensitivity analysis and model validation as it was unclear whether there were any changes based on these activities. We continue to recommend these to EPA with the revised model.

One of the most important issues we noted in January and continue to request is a demonstration that the model is in accordance with the known MOA for perchlorate. That MOA, laid out by the NRC (2005) identifies IUI as the first measureable effect; if IUI is sufficiently high and for a long enough duration, only then could the first adverse effect (hypothyroidism) occur. EPA's previous model reported changes to thyroid hormones that occurred before IUI. There is no study to support this

[1] The Perchlorate Study Group is supported by Aerojet Rocketdyne, American Pacific Corporation, Lockheed Martin, and Orbital-ATK.

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outcome. The current model should be examined to determine whether IUI occurs at a dose that is both consistent with the literature or occurs at doses lower than changes in thyroid hormones. This threshold provides a lower limit below which changes in thyroid hormone would not occur.

2.1.1 Iodine intake

EPA's expanded range of iodine intakes is appreciated. We have two issues of concern. First is that the lower levels have greater uncertainty due to the underlying data sets. The model has not been demonstrated to be able to predict iodine deficiency. There are study populations available for this critical check on the model (New Zealand, etc.).

The results of the BBDR highlight that the greater public health issue is iodine deficiency in pregnancy rather than perchlorate exposure. Studies have repeatedly demonstrated that perchlorate exposure contributes less than 2% of IUI given a normal diet that includes nitrate and thiocyanate.

Second is that, in setting regulatory levels for other contaminants, EPA has never used a nutritionally-deficient population as the most sensitive subpopulation. The results of the BBDR highlight that the greater public health issue is iodine deficiency in pregnancy rather than perchlorate exposure. Studies have repeatedly demonstrated that perchlorate exposure contributes less than 2% of IUI given a normal diet that includes nitrate and thiocyanate (Bruce *et al.*, 2013; Tarone *et al.*, 2010) and remedying iodine deficiency would have the greatest impact on public health (OIG, 2010). The EPA Draft Report (2017) recognizes the impact of iodine intake compared to perchlorate:

> …there is a significant drop in fT4 and increase in TSH with decreased iodide intake in the absence of perchlorate exposure. Comparing the predicted fT4 and TSH levels at zero dose of perchlorate in Table 2 (170 µg/day iodine intake) and Table 3 (75 µg/day iodine intake; a 56% drop in iodine intake from the median level) shows approximately a 16 to 17% drop in fT4 and between approximately a 44% to 58% increase in TSH, depending on the gestational week of interest.

There is a high correlation between iodine intake and perchlorate intake (Steinmaus *et al.*, 2016; Lee *et al.*, 2017). The assumption of iodine intake for modeling is used independently of realistic perchlorate exposures. In reality, it's not likely to have high perchlorate and low iodine intake on a regular, daily basis because intake is so highly correlated. These assumptions lead to unrealistic modeling results that are overly conservative.

2.1.2 TSH feedback

The hypothalamic-pituitary-thyroid axis is a tightly controlled hormonal negative feedback loop. It was an omission from the original model that we noted. The TSH feedback loop was added to the revised model. Although it is likely that actual feedback in a human is more nuanced and variable than the modeled feedback, EPA notes,

> Additionally, Hadlow *et al.* (2013) demonstrated that the relationship between TSH and T4, while a consistently decreasing function, is variable across the population with factors such as genetics, subclinical thyroid disease, age, and gender contributing to this variability. Thus, the ability of the thyroid to respond to TSH after perturbation by perchlorate probably varies across the population. The association between perchlorate and diminished T4 in the face of elevated TSH (Steinmaus, *et al.*, 2013; Steinmaus, *et al.*, 2007; Blount *et al.*, 2005) suggests that certain segments of the population (low iodide, smokers) respond more weakly than others.

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Our main concern is that the modeled individual has a high TSH and average fT4. This models a person who responds more weakly to TSH. EPA states, "this choice is based on an assumption that sensitive individuals with high TSH and average fT4 exist because the stimulus strength of TSH is proportionally weaker." Although this person may exist, the purpose of the BBDR is to estimate the response of an average person. As described in Chapter 4.0 of the EPA Report, the model output is used as the average value and a distribution is predicted around that average individual. A model should not contain multiple conservative inputs as this will lead to an uncertain amount of conservatism that is unrealistic.

2.1.3 Recommendation

A scientifically-sound and transparent model can help inform the MCLG process. We recommend the Agency improve the transparency, present validation of the model, and provide a clear understanding of the model limitations.

2.2 Hypothyroxinemia

Neither the NRC, nor any other authoritative body, lists hypothyroxinemia as precursor to hypothyroidism.

EPA has chosen to use hypothyroxinemia as an endpoint based on the recommendation of its Science Advisory Board (SAB). The purpose of the SAB was to evaluate approaches that EPA was exploring for use in developing an MCLG. No thyroid endocrinologists were members of this expert panel, which perhaps explains why the panel established as an endpoint a concept that is little more than a research construct. The ATA, in its *2017 Clinical Guidelines for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum* states "Isolated hypothyroxinemia should not be routinely treated in pregnancy." In contrast the NRC's evaluation of perchlorate in 2005 included several thyroid endocrinologists who were very clear in their determination that hypothyroidism was the critical adverse effect for perchlorate exposure. There is no new scientific information that would tend to undermine NRC's conclusion.

Neither the NRC, nor any other authoritative body, lists hypothyroxinemia as precursor to hypothyroidism. The Agency has modified the accepted MOA for perchlorate. We are not aware of any perchlorate study, animal or human, where hypothyroxinemia is a measured endpoint to support this modification.

Finally, the BBDR model can only predict levels of total T3 (TT3) and total T4 (TT4). Although fT4 is not mechanistically modeled, EPA uses a fraction of TT4 to define fT4 levels. Diagnoses based on thyroid hormone measures are well-defined clinically. Subclinical hypothyroidism is elevated TSH with normal levels of fT4. Hypothyroxinemia is defined as low fT4 with normal levels of TSH. Overt hypothyroidism is considered an adverse effect and, if it occurs in a pregnant woman or infant, may affect the developing brain. Hypothyroidism is defined as sustained elevated TSH and low fT4. The NRC recognized hypothyroidism as the first adverse effect on the dose-response continuum (NRC, 2005).

2.2.1 There is no reference range for fT4

Although there is a reference range for TSH levels in different stages of pregnancy and in infancy, an analogous reference range does not exist for fT4. In the Final Peer Review Report of the model (Versar, 2017), it states,

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> Free T4 assays, as noted in the text, are poorly concordant with each other in pregnancy and some assays lose the expected inverse relationship with serum TSH values… It is generally recommended that normal thyroid function reference ranges be assay-specific, and that they should be defined in populations of individuals with no known history of thyroid disease, with adequate iodine intakes, and with negative thyroperoxidase (TPO antibodies).

The reason is that different laboratories have variations in techniques and populations that make direct comparisons impossible. Therefore, in general, a laboratory will consider a cutoff for "low" or "high" based on the percentile in the batch it is testing. This cutoff is commonly the lowest 2.5th percentile, 5th percentile, or 10th percentile. There is no recommendation by any authoritative medical body on the appropriate cutoff.

Although in the previous Peer Review of the model EPA chose to define provisional reference ranges for fT4, in the current document, EPA avoids this issue by using the model to estimate changes in fT4 which are mathematically associated with neurodevelopmental outcomes in Approaches 1 and 3. However, in the population shift approach (Approach 2), EPA defines hypothyroxinemia as the lowest 10th percentile on the calculated distribution based on the 50th percentile output from the BBDR model. That value is 8.8, 8.78, and 8.63 pmol/L for weeks 12, 13, and 16, respectively. The concern here is that these cutoffs are not applicable to testing in the population and cannot be diagnosed or experimentally tested. This cannot be validated in any meaningful way.

2.2.2 Hypothyroxinemia is not an adverse effect

Transient hypothyroxinemia is not uncommon in pregnant women and severely premature infants (born at less than 28 weeks). In an individual, hypothyroxinemia is not considered adverse. The ATA, American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) do not recommend treatment for hypothyroxinemia. The Endocrine Society suggests best judgement by the treating physician, however, does not recommend treatment in third trimester women (Furnica *et al.*, 2015).

Hypothyroxinemia as an endpoint to measure the effects of an environmental contaminant is questionable, particularly in pregnancy. There is a necessary rise in TT4, but also increased binding due to TBG, HCG, and other serum proteins. This results in hypothyroxinemia, but no change in circulating T3 levels with T3 being the active hormone. It is hypothesized that hypothyroxinemia is an adaptive response by the body to maintain adequate hormone level (Furnica *et al.*, 2015).

2.2.3 Treatment for hypothyroxinemia has not been shown to impact neurodevelopment

There is no study we are aware of that reports that perchlorate exposure causes hypothyroxinemia. The Agency assumes that it does. The Agency must provide the scientific support to justify including the endpoint of hypothyroxinemia and its relationship to neurodevelopment. Using fT4 solely from output of a BBDR model to predict a disease that the ATA states in their guidelines is not to be treated is not scientifically defensible.

Interventional studies have reported that treatment of the mother with synthetic T4 does not improve outcome compared to untreated (Lazarus *et al.*, 2012; Casey *et al.*, 2017). Importantly, these studies evaluate hypothyroxinemia in the first trimester with outcomes at up to 8 years of age. This is the period of interest based on the BBDR model results.

The first Peer Review report supported this and stated

> Despite the observational data suggesting a link between early gestational maternal hypothyroxinemia and adverse child developmental outcomes, there are now two randomized

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clinical trials...which demonstrate no benefit of levothyroxine treatment for maternal hypothyroxinemia on child IQ. (It is worth noting that both of these trials were limited by relatively late initiation of therapy; at 13 weeks in CATS and at 17 weeks gestation in the Casey study.) Given both the lack of interventional data demonstrating treatment benefit, and the challenges of establishing maternal free T4 reference ranges and treatment targets, current clinical guidelines (including newly published updated guidelines from the American Thyroid Association…) largely recommend against levothyroxine treatment for isolated maternal hypothyroxinemia."

2.2.4 Recommendation

We recommend the Agency use the BBDR model to consider hypothyroidism as the adverse effect.

2.3 Neurodevelopmental Testing

Assessing the neurodevelopmental outcomes from chemical perturbations during neurodevelopment is an area of study that is divided into many sub-disciplines. The documents and approaches the Agency has released simplifies a very complex area of study. In EPA's documents there are two components to examine carefully: the time of testing during gestation and the type of neurodevelopmental test given to the offspring.

2.3.1 Maternal thyroid testing

Neurodevelopment, or the controlled process by which the nervous system develops, has the potential to be affected by maternal and paternal factors. Neurodevelopment begins to occur about two weeks after conception in humans and continues until birth and up to early adulthood (Figures 1 and 2). The timing of neurodevelopment is documented, thus giving rise to windows of vulnerability to environmental insult during development (Figure 1 and 2).

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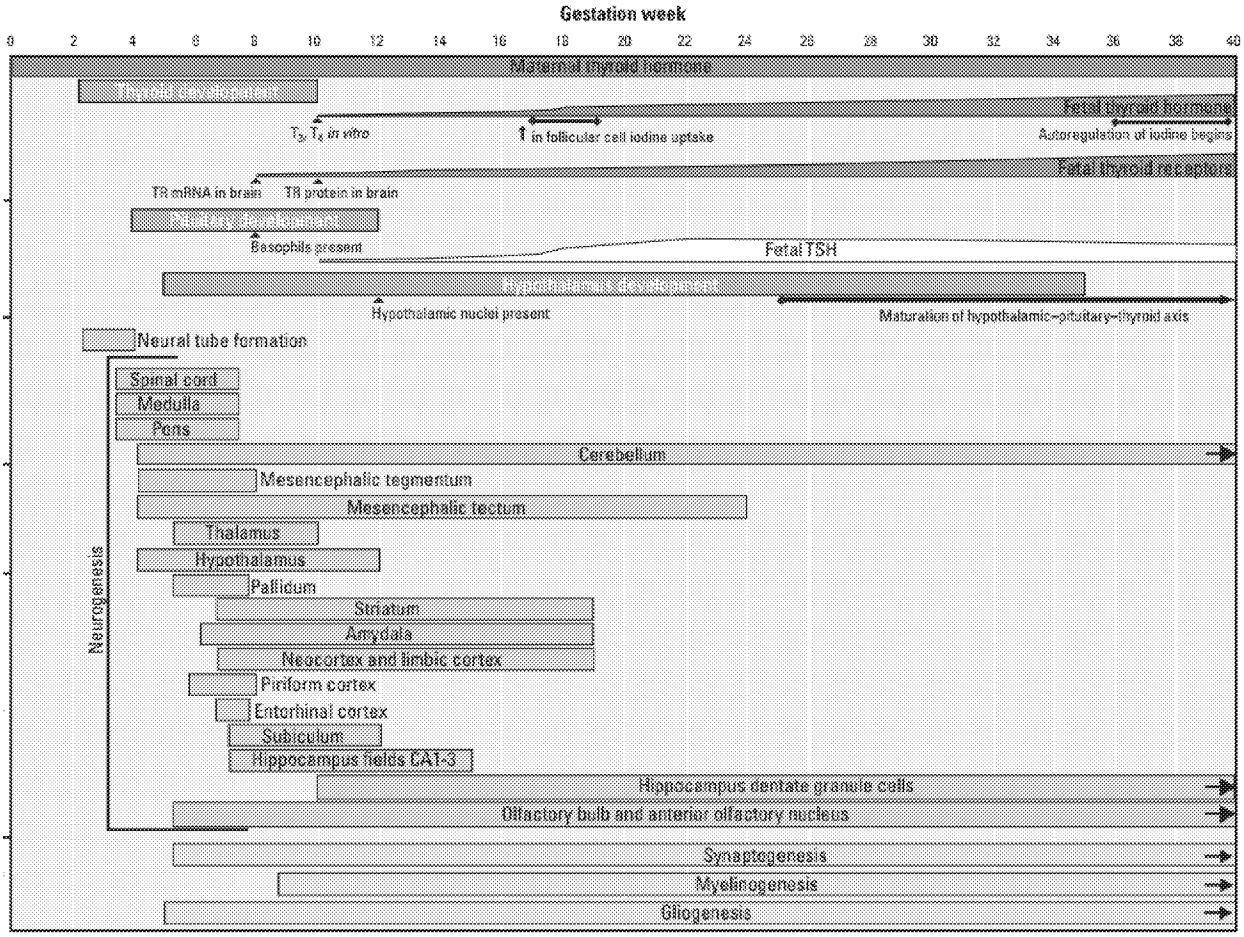

FIGURE 1 HUMAN *IN UTERO* THYROID AND NEURODEVELOPMENTAL TIMELINE
Timeline of human neurodevelopment. From Howdeshell (2002).

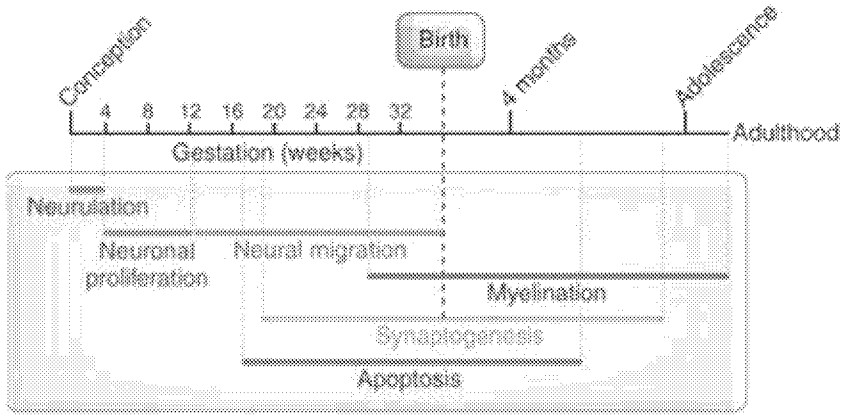

FIGURE 2 HUMAN NEURODEVELOPMENT FROM CONCEPTION TO ADULTHOOD
Timeline of major events in brain development from conception through adulthood. From Tau and Peterson (2010).

In the studies used by EPA, there is an attempt to quantify the association between a single measure of thyroid hormone in the first or second trimester with the neurodevelopment of her offspring over a year and up to 10 years after birth. During this period, there are many factors that could affect

development. There are other *in utero* conditions, exposures, maternal stressors, and nutrition that may contribute to variations. There are birth conditions, such as delivery complications, caesarian versus vaginal birth, or season of birth. There are post-natal conditions that may contribute. There is no way of knowing which of these things might affect neurodevelopment and to what extent. Statistically, factors that may affect both the variables and the outcome can be controlled for. However, in these studies, only a limited number of factors are considered, if any at all.

Severe iodine deficiency can cause neurodevelopmental effects via the reduction in thyroid hormones. However, the iodine status of the study populations used by EPA are not given except to say they are assumed to be iodine sufficient (Korevaar *et al.*, 2016; Pop *et al.*, 1999; Pop *et al.*, 2003; Finken *et al.*, 2013). Vermiglio *et al.* (2004) used a study population that is marginally iodine deficient and the control group is only marginally iodine sufficient. In Korevaar *et al.* (2016), the authors state,

> Another potential limitation of our study is the fact that we only had iodine data available from a small subset of 672 women (table), and iodine status could adversely affect both thyroid function and child brain development. Although this study was undertaken in a population with proven iodine sufficiency, we should note that iodine-deficient women, and those with high iodine intake, could still be present in the study population.

The Pop *et al.* (1999, 2003) studies did not measure iodide, but assume their population was sufficient based on previous studies. The authors state:

> Although 24-h iodine intake was not assessed either, previous population studies have reported sufficient iodine intake in the general population in this area, while other studies questioned whether this daily intake was sufficient for pregnant women with regard to the fetus.

EPA recognizes this weakness and writes:

> The data from all papers with the exception of Vermiglio *et al.* (2002; Italy) are from the Netherlands and are being considered for use in to inform the derivation of an MCLG for the United States. There is no reason to believe that the impact of fT4 on neurodevelopment would differ by country, unless there is a substantial difference in iodine intake. Unfortunately, exact data on iodine intake levels in the Pop *et al.* (1999, 2003) papers are not provided. However, the authors cite two studies on iodine levels in the general population of the Netherlands. Rees-Wortelboer *et al.* (1987) studied a sample of 253 Dutch women aged 23-32 and found a mean urinary iodide excretion (corrected for creatinine) of 115 μg/g creatinine. Brussaard *et al.* (1997) compiled studies on iodine supply after the introduction of iodized salt in the Netherlands in 1982. The researchers found that estimates of the mean iodine intake in women under the age of 65 ranged from 135 to 149 μg/day. An additional study of Dutch food consumption data from 1997-1998 by Verkaik-Kloosterman *et al.* (2010) estimated that the median iodine intake of adult women in the Netherlands was 204 μg/day. Iodine intake levels appear to be similar in the United States.

Other issues include measurements of clinical chemistry. An example is iron deficiency. A study in Swiss pregnant women reported that iron status predicts higher TSH and lower thyroid hormones (Zimmerman *et al.*, 2014). None of the neurodevelopmental studies control for or measure iron status.

2.3.2 Animal studies on neurodevelopment

EPA does not define neurodevelopment or what the neurodevelopmental tests are intended to document. Neurodevelopmental assessments require rigor and focus. The Agency is not clear on this and excludes key animal studies that provide useful information.

While the Agency suggests a process from perchlorate exposure to neurodevelopmental outcome, there is no science to support that health effects from perchlorate exposure progresses according to EPA's hypothesized MOA.

First, the NRC MOA of perchlorate is well understood and is not contested. Perchlorate affects the thyroid by competitively inhibiting iodide uptake to the thyroid through interaction with the sodium iodide symporter (NIS). This inhibition is reversible and not considered adverse. With sustained and significant inhibition—estimated to be about 70% inhibition for several months or more (NRC, 2005)—hypothyroidism could occur. Changes in thyroid hormone cannot occur without IUI; however, changes in thyroid hormones are not an inevitable consequence of IUI, that is, with cessation of exposure, no adverse health effects would occur.

Animal studies on perchlorate and neurodevelopment consistently report no significant changes in the developmental endpoints measured even with doses much greater than in human studies.

Second, there are several animal studies evaluating perchlorate exposure prior to and during pregnancy with a full battery of neurodevelopmental outcomes (Bekkedal *et al.*, 2000; York *et al.*, 2001; York *et al.*, 2004; York *et al.*, 2005). The endpoints reported for each study are summarized in Table 1. These were controlled animal experiments with doses ranging from 0 (controls) to 30 mg/kg-d (30,000 µg/kg-d or 1,050,000 ppb), dosed orally during gestation. These studies all report no significant changes in the developmental endpoints measured. This information is not presented in the EPA documents and we recommend it be included. Some of the neurodevelopmental tests include tests that scientist use to assess intelligence, motor, maturation and sensory outcomes.

The literature on untreated thyroid deficiency during pregnancy consistently demonstrates that hearing deficits are the most sensitive neurodevelopmental outcome. As noted below, no test of intelligence, motor, maturation, auditory startle, or other variable was shown to be different from controls at doses as high as 30 mg/kg-d.

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TABLE 1 ANIMAL STUDIES ON NEURODEVELOPMENT AND ENDPOINTS REPORTED

Study	Doses	Endpoint	Result
Bekkedal *et al.*, 2000	0, 0.1, 1.0, 3.0, 10 mg/kg-d	General locomotor activity	No significant change in general locomotor activity due to prenatal and neonatal perchlorate exposure
York *et al.*, 2001	0, 0.3, 3.0, 30 mg/kg-d	F1 generation brain weights	No significant changes in developmental parameters were observed
York *et al.*, 2004	0, 0.1, 1.0, 3.0, 10 mg/kg-d	Juvenile brain weights, morphometry, and neuropathology (PND 12); Adult regional brain weights (PND 89), morphometry, and neuropathology; Passive avoidance and water maze testing, motor activity and auditory startle habituation	No effect on body weights, feed consumption, clinical observations, or sexual maturation of pups; No neurodevelopmental effects as evaluated by passive avoidance, swimming water maze, motor activity, and auditory startle; Significant decrease in follicular lumen diameter at ≥1 mg/kg-d (males)
York *et al.*, 2005	0, 0.1, 1.0, 3.0, 10 mg/kg-d	Motor activity (PNDs 14, 18, and 22) and juvenile brain weights, neurohistopathological examinations, and regional brain morphometry (PNDs 10 and 22)	Authors conclude that the NOAEL for maternal toxicity was greater than 10 mg/kg-d and the NOAEL for pup toxicity was 0.1 mg/kg-d based on the thyroid morphometric and histopathologic findings

2.3.3 Human neurodevelopmental tests

The purpose of testing is to identify individuals who require specialized care and learning due to a developmental delay or disability. The validation group may be a group at a specific age from a specific country that may not correspond to the current US population.

In documents provided, the Agency is using four different tests of "neurodevelopment"; they do not measure the same endpoint. The tests used as a metric in these studies include intelligence quotient (IQ), psychomotor development index (PDI), motor development index (MDI), and the standard deviation of reflex time. A summary of these tests, what they measure, and the age to be tested, along with other characteristics is presented in Table 2.

There are fundamental issues to be addressed with using human neurodevelopmental tests that include the reliability, the variability, the test population, and the age the test was administered.

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TABLE 2 NEURODEVELOPMENTAL TESTS IN THE STUDIES USED BY EPA

Test	Description	Intended Age	Reliability	Variability
Snijders-Oomen Niet-Verbale Intelligentie Test IQ (test used in Korevaar *et al.*, 2016)	Subtests: Mosaics, which assesses spatial visualization abilities, and Categories, which assesses abstract reasoning abilities	2.5-7 median age of 6·0 years (95% range 5·6–7·9 years)	The mean reliability of the subtests of the SON-R 2.5-7 is 0.72 and the reliability of the total IQ score is 0.90. (wiki)	Median of 100, no SD found
Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) (test used in Vermiglio *et al.*, 2004)	Verbal skills and performances in the following areas: general information, general comprehension, arithmetic, similarities, vocabulary, digit span, picture completion, picture arrangement, block design, object assembly, coding, and mazes	6-16	Subtest reliabilities (expressed as internal consistencies for all but the speeded subtest of Symbol Search and Coding) are moderate to excellent (.61 to .92). The consistency of IQS and Indices is very good to excellent (.80 to .97). Subtest stability coefficients, based on 353 children subdivided into three age groups, are adequate (.56 to .89). IQ and Index stability is mostly good to excellent (.74 to .95; only one coefficient below .80). Interrater reliabilities for selected Verbal Scale subtest are excellent (all greater than .92). (http://cps.nova.edu/ ~cpphelp/WISC-3.html)	For index and FSIQ scores, M = 100 and SD = 15
Bayley Scales of Infant Development PDI (used in Pop *et al.*, 1999, Pop *et al.*, 2003	Gross motor development	1-42 months 10 month olds (99) 1 year olds (03) 2 year olds (03)	Psychosocial factors, demographic features, life-style habits during pregnancy (smoking, alcohol), breastfeeding and the occurrence of stressful life events.	Mean of 100 and a standard deviation of 16 (Pop *et al.* state "these are still considered reliable")

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Test	Description	Intended Age	Reliability	Variability
Bayley Scales of Infant Development MDI (used in Pop *et al.*, 1999 Pop *et al.*, 2003)	Functioning such as hand-eye coordination, manipulation, understanding of object relations, imitation, and early language development.	1-42 months 10 month olds (99) 1 year olds (03) 2 year olds (03)	Scale composite average reliability coefficients ranged from .91 (Cognitive) to .93 (Language), whereas subtest average reliability coefficients ranged from .86 (Fine Motor subtest) to .91 (Expressive Communication and Gross Motor subtests). Within specific subtests, the lowest reliability coefficients (e.g., .71) were obtained in the younger age groups (e.g., 1-5 months) within the Receptive and Expressive Communication subtests. The average reliability coefficients for the special groups included in the sample were all greater than .94.	No information found
Amsterdam Neuropsychological Tasks (ANT) SD of reaction time (used in Finken *et al.*, 2013)	Attention, information processing, executive function, and visuospatial perception	3-47; The four parts of the test given are for use in ages 4+ subjects were 5.7 +/- 0.5 years	No information found.	Units are ms; a one unit drop is unclear as an adverse event

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2.3.3.1 Isolated test results are questionable

The results of a single test were never intended to be used to define the effect of small changes in thyroid hormones. Along these lines, it is difficult to portray what level of predicted change is adverse either to the individual or the population. EPA treats a one point change in the various metrics as significant; however, one point on the PDI is different than one point on the standard deviation of reaction time. EPA states:

> …considering the analysis for Finken *et al.* (2013), it is difficult to ascertain the true implications of a change in the standard deviation of reaction time, the endpoint with which there is a significant association with maternal fT4 levels.

The tests were also not meant to be considered in isolation or for differentiating small changes between individuals. For example, in the handbook of the Snijders Ooomen test, it states that:

> …administration of the test will not take place in isolation, but within a framework of discussions with, and observation of child and parent(s), and of information from schools or family doctors. An intelligence test is also frequently administered in combination with other developmental tests."

Similarly,

> The Amsterdam Neuropsychological Tasks Program (ANT) is intended for systematic evaluation of attention and information processing, ie. the basic conditions for the implementation of complex cognitive processes (including sustained, focused and divided attention, key aspects of executive function - such as attention-based flexibility, inhibition and work memory - simple and complex visual motor coordination, recognition of faces and emotions in the face and in the voice, frustration tolerance)."
> http://www.antprogram.nl/index.php

Thus, these tests must be administered with care by seasoned psychologists. Regarding use as toxicological endpoints, in a 1999 Society of Toxicology workshop (Bellinger, 1995) focusing on the use of neurodevelopmental testing in toxicological research, the participants concluded:

> In human neuropsychological work, many of the most commonly used tests were developed in the context of clinical evaluation, where the primary goal is to identify clinically significant impairments among patient groups (e.g., individuals with CNS insults such as traumatic brain injury, stroke, tumors, infections, etc.). Many domain-specific tests were not designed to detect small differences in performance within the normal range. In this respect, apical tests, which were developed to permit inferences about individual differences along the entire spectrum of performance, may be better suited than domain-specific tests to the task of detecting subtle impacts of toxicant exposures on neuropsychological function (Bellinger, 1995).

2.3.3.2 Tests are not predictive of adult intelligence

The Agency is evaluating whether exposure to a pregnant woman will cause adverse effects in her offspring. When tests are given to young children, the tests are not predictive of adult intelligence. Thus, these tests are not indicative of any long-term deficits. The study by Pop *et al.* (2003) accurately notes:

> …assessment of infant development at an early age still has only a limited value regarding the prediction of a child's abilities once it has reached school age. This is especially true of

> Bayley scores at 1 year of age, while at 2 years of age, these scores are related to functioning at 5 years of age.

And,

> In one study, we found a relationship between impaired infant development at 10–12 months and maternal hypothyroxinaemia during early gestation, but infant development at this early age still has only a limited value regarding the prediction of a child's abilities at later age.

2.3.3.3 Confounders are not adequately controlled

Clear confounders that must be controlled for very carefully are parental interaction quality and quantity, socio-economic status (SES), and education. Hart and Risley (1995), in their groundbreaking study, demonstrate that early language learning is a better measure of cognitive ability than any other measure. They conclused that the acquisition of language is the best measure of cognitive development as it can be accurately measured, and that a family environment with frequent and deliberate interaction with children is critical to neurodevelopment. When analyzing their dataset, Hart and Risley determined that SES was highly correlated with a child's language development.

Rigorous analysis of other confounders is necessary to assess the reliability of the study. One report noted:

> There is evidence that education has the greatest impact on performance in the cognitive tests used in neurotoxicity research (Anger *et al.*, 1997)… Clearly, educational background has a large impact on the cognitive tests used in this field, as does age, and to a lesser extent, gender (Anger *et al.*, 1997). Thus, cognitive research in human populations must control these factors in the groups under study, not in the analysis.

The use of studies without well-controlled study designs, limits the conclusions that can be derived and limits their use in regulatory decision making.

2.3.3.4 Clinical significance is unclear

Small changes between groups or even individuals are not likely to be meaningful or even persistent. For example, in testing two toddlers at age two where one has an IQ of 100 and the other has an IQ of 96, several observations can be made: 1) this difference is not a clinically-significant difference, 2) the ability of most behavior testing to predict future intelligence is poor, and 3) testing a two-year-old at the start of their language development is not meaningful and can be affected for numerous reasons.

If a variable, such as IQ, has a standard deviation of 15 points, a difference of 4 points is within the natural background variability. EPA has not provided a scientific rationale to support that differences within the inherent variability of the measure are meaningful.

2.3.3.5 The EPA uses studies with populations different than those in the US

One of the main concerns with the use of EPA's studies is their applicability to the US population. The US is iodine sufficient. There may also be significant demographic, ethnic, nutritional, and genetic differences between the study population and the population these data are applied to. The true differences cannot be known.

In particular, the study by Vermiglio *et al.* (2004) used a small population that was not randomly selected. The data were collected over a ten year period and included both moderately iodine

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deficient and moderately iodine sufficient age-matched mothers. The children in the study were also unusual in that there was a high incidence of goiter and ADHD (the focus of the study) among the subjects. At the time of conception, almost 25% of school-aged children in the moderately iodine deficient area had goiter. The intelligence test in this study was not given as a primary outcome measure to assess hypothyroxinemia, but as a secondary evaluation to rule out mental retardation. Eleven out of the 16 subjects in the moderately iodine deficient are were diagnosed with ADHD.

There may be other variables in thyroid status that suggest these populations are not applicable to the US population. When compared to a US population (Mortensen *et al.*, 2016), the TSH concentrations are similar in these populations, but the fT4 concentrations are lower in the Finken *et al.* (2013) and two Pop *et al.* (1999, 2003) studies (Table 3). The fT4 levels are similar to those in the Korevaar *et al.* (2016) and Vermiglio *et al.* (2004) studies.

TABLE 3 MEASURES OF FT4 AND TSH IN STUDY POPULATIONS

Study	Location	Date Collected	N	fT4 concentration (pmol/L)	TSH concentration (mU/L)	blood collection timing
Korevaar *et al.*, 2016	Rotterdam, Netherlands	2002-2006	3839	**14.9 (10.2–22.4)** median (95% range)	**1.35 (0.05-4.96)**	13·2 weeks (95% range 9·8–17·5)
Finken *et al.*, 2013	Amsterdam, Netherlands	2003-2004	1765	**9.6 (8.8 –10.4)** mean (SD)	**1.2 (0.8-1.7)** mean (SD)	12.9 w (median 90 d IQR 83-100)
Pop *et al.*, 1999	Veldhoven, Netherlands	1994	220	**13.1 (2.6)** mean (SD)	**0.14–2.2** Reference range for study	12 weeks (no range)
Pop *et al.*, 2003	Eindhoven, Netherlands	1997-1998	235	**12.1 (15.4–19.0)** mean (90% range); first group; mean not given for whole cohort	**0.15–2** Reference range for study	12 weeks (no range)
Vermiglio *et al.*, 2004	Sicily, Italy	1990-1992	27	**14.4 (1.7)** mean (SD)	**0.4–4.0** Reference range for study	Week 20
Mortensen *et al.*, 2016	United States	2009-2010	359	**14.3 (13.9, 14.5)** Arith mean (95% CI)	**1.46 (1.37-1.56)** Geo mean (95% CI)	Third trimester
ATA Reference Range				**13.9-23.4 (week 14) 11.1-19.7 (week 20)**	**<4.0**	

The ATA also notes there are differences in Dutch populations from US populations in stating:

> Initial studies of pregnant women in the United States and Europe first led to recommendations for a TSH upper reference limit of 2.5 mU/L in the first trimester and 3.0 mU/ L in the second and third trimesters. However, more recent studies in pregnant women in Asia, India, and the Netherlands, have demonstrated only a modest reduction in the upper reference limit.

This suggests that women in the Netherlands may have different ranges of thyroid hormones which would affect the slope of any regression based on data from these populations. Even if it were acceptable to use thyroid tests to predict decrements in neurodevelopment, it is not clear that these

populations would be appropriate for prediction in US populations based on either thyroid hormone measures or neurodevelopmental testing.

2.3.4 Recommendation

The literature supporting the association between hypothyroxinemia and adverse neurodevelopmental outcomes is equivocal at best, and lacks predictive power as the basis of a regulation. Consistent with the established perchlorate MOA and the weight of scientific evidence, the Agency should consider neurodevelopmental effects as downstream from hypothyroidism.

3.0 THE THREE APPROACHES

Two approaches are detailed in the main document. However, we note that a third approach is presented in detail in Appendix C. The third approach is scientifically weaker than Approach 1. We do not believe an approach confined to the Appendices should be used by EPA; however, we consider it here on the off chance that it is intended to be a serious approach.

> Approach 1: The BBDR model is used to estimate maternal fT4 levels with different intake levels of iodine and perchlorate. A change in fT4 is used to predict neurodevelopmental deficits in offspring based on a subset of epidemiological studies.
>
> Approach 2: The BBDR model is used to predict a population shift comparing the number of women who would be considered hypothyroxinemic under two scenarios.
>
> Approach 3: The results of a single study are used to predict a relationship between perchlorate and maternal fT4. A change in fT4 is used to predict neurodevelopmental deficits in offspring based on only one epidemiological study.

3.1 Approach 1: BBDR + Neurodevelopment

Approach 1 uses a two-stage approach: 1) BBDR to estimate changes in maternal fT4, followed by 2) the use of a subset of epidemiological studies to link maternal thyroid hormone levels to neurodevelopmental outcomes in offspring.

This approach depends on the use of realistic inputs and the ability of the BBDR model to accurately predict fT4 levels, and the use of a set of epidemiological studies selected through a systematic literature review.

3.1.1 Hypothyroxinemia studies that were used

One of the main criticisms during EPA's first Peer Review was the lack of transparency in the literature review. This documentation on the literature review for hypothyroxinemia studies is a great improvement. It was a targeted literature review as EPA reports:

> Based on the recommendations of previous peer review panels, EPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes. For this reason, EPA did not conduct a complete, systematic review of the body of literature on this topic.

EPA documents its three step approach that resulted in fifteen Group 1 studies; these studies were chosen because they had continuous data and measured first trimester fT4. However, the final five studies selected for use in EPA's assessment were only those that had the association that EPA was seeking (positive association between fT4 and IQ). EPA states,

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That is, studies were identified that found an association between a continuous measure of fT4 and neurodevelopment and had all the requisite data to perform additional analysis to potentially inform the derivation of an MCLG.

Aspects of the final five studies have been discussed in sections 2.2 above. Based on EPA's own inclusion/exclusion criteria, several of EPA's studies are misclassified:

- Vermiglio *et al.* (2004): The regression presented in this study, and used by EPA, is based on week 20 thyroid hormone measures. This study should have been classified as Group 3 based on the incorrect measurement period.
- Gyllenberg *et al.* (2016): This study presents odds ratios that cannot be used as continuous data. It should have been classified as Group 2 based on the presentation of results.
- Heinrichs *et al.* (2010): This study presents odds ratios that cannot be used as continuous data. It should have been classified as Group 2 based on the presentation of results.
- Velasco *et al.* (2009): This study presents thyroid hormone data collected in the third trimester. This study should have been classified as Group 3 based on the incorrect measurement period.

3.1.2 Hypothyroxinemia studies that were not used

EPA ignored the weight of evidence in favor of using studies that only showed a positive relationship.

The remainder of the Group 1 studies generally do not report an association between maternal hypothyroxinemia and adverse neurodevelopmental outcome. When evaluated by time of serum collection, it is clear that EPA only chose studies that demonstrated a positive association (Table 4). Although there are more studies that demonstrate that no significant relationship exists, these studies were disregarded.

TABLE 4 POSITIVE AND NEGATIVE GROUP 1 STUDIES BY SAMPLE COLLECTION

	First Trimester (weeks 0-13)	Second Trimester (weeks 14-26)	Third Trimester (weeks 27-40)
Positive Studies	**Finken *et al.* (2013)** **Korevaar *et al.* (2016)** **Pop *et al.* (1999)** **Pop *et al.* (2003)**	None	None
Negative Studies	Moleti *et al.* (2016) Noten *et al.* (2015) Oken *et al.* (2009)	Chervier *et al.* (2011) Ghassabian *et al.* (2014b) Modesto *et al.* (2015) Román *et al.* (2013)	None

Studies by Gyllenberg, Heinrichs, Vermiglio, and Velasco have been removed as discussed in Section 3.1.1
BOLD studies were used by EPA in its analysis.

As discussed in section 2.2, neurodevelopmental testing has greater predictive power if given later in childhood. If we further categorize these remaining 11 studies by when the neurodevelopmental tests were conducted, we see that the negative studies overwhelmingly were given in later childhood years compared to the positive studies (Table 5). Taken together, it appears that EPA ignored the weight of evidence in favor of using studies that only showed a positive relationship.

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TABLE 5 POSITIVE AND NEGATIVE GROUP 1 STUDIES BY TESTING AGE

	Birth to <1 year old	1 to <5 years old	5-12 years old
Positive Studies	**Pop *et al.* (1999)**	**Pop *et al.* (2003)**	**Finken *et al.* (2013)** **Korevaar *et al.* (2016)**
Negative Studies	Oken *et al.* (2009)	None	Moleti *et al.* (2016) Noten *et al.* (2015) Chervier *et al.* (2011) Ghassabian *et al.* (2014b) Modesto *et al.* (2015) Román *et al.* (2013)

Studies by Gyllenberg, Heinrichs, Vermiglio, and Velasco have been removed as discussed in Section 3.1.1
BOLD studies were used by EPA in its analysis.

3.1.3 fT4 testing

Measures for fT4 are generally conducted in serum and since the 1970s, technological advances in radioimmunoassay (RIA), immunometric assay (IMA), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) have continued to improve the sensitivity, reproducibility, detection levels, and incidence of errors. There are significant differences between test manufacturer protocols which may be in excess of the biological variation in fT4 levels (Spencer, 2017). Measures for fT4 are generally conducted in serum. Currently, serum-based immunoassays and LC-MS/MS techniques are available for measuring total and free thyroid hormones.

Tests for fT4 are generally used for screening followed by TSH screening or after TSH screening to confirm a diagnosis. Taken alone, the tests are less reliable. Even most current tests underestimate true fT4 values (Figure 3). An evaluation of current fT4 immunoassays shows significant between-method variability and tend to bias lower than the reference measurement procedure (RMP; equilibrium dialysis-dilution-mass spectrometry; Spencer, 2017)

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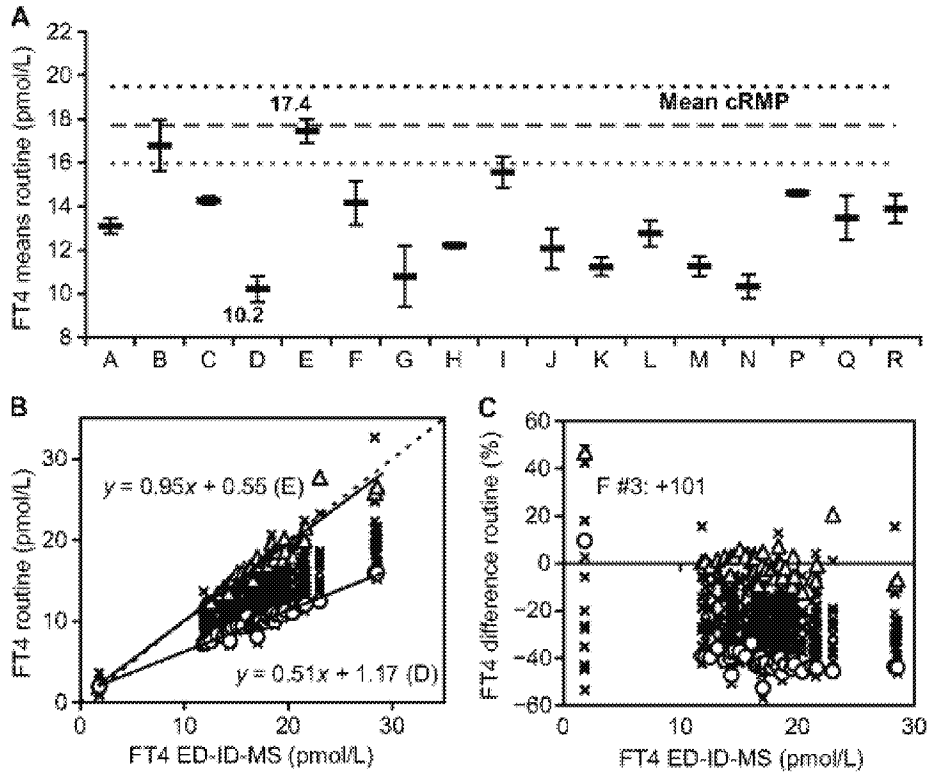

FIGURE 3 BETWEEN ASSAY COMPARISON OF FT4 MEASURES IN HEALTHY EUTHYROID SUBJECTS
Between Assay Comparison of FT4 Measurements in Healthy Euthyroid Subjects. A=FT4 assay means versus the mean by the reference measurement procedure (RMP; equilibrium dialysis-dilution-mass spectrometry). Different assays are coded A-O on the x axis. The dotted lines represent mean +/- 10% of the RMP ED-ID-MS). B=FT4 scatter plot (x=mean of the RMP vs. y= mean of 6 singlicate results per assay. Line of equality indicated by dotted line. The results for the most deviating assays are indicated by circles and triangles; all other assays are indicated with the same symbol, X. C=FT4 percent-difference plot indicating the strongest negatively (circles) and positively (triangles) biased assays. From Spencer (2017).

The type and brand of fT4 assay used in the five studies that were the focus of EPA's assessment are listed in Table 6. All five use different test packages and direct comparison is not recommended. It is not clear that a parallel relationship would persist between two different tests as there may be differences in sensitivity at high or low regions of the reference range. Therefore, statistical associations that presume that changes in fT4 would be consistent are unsupported by the analytical capabilities of the underlying tests.

Additionally, there are distinct differences in local populations that led the American Thyroid Association (ATA) to recommend population based reference ranges for pregnant women. The most recent ATA guidelines state:

> When possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider's practice. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPOAb status.

TABLE 6 TYPES OF FT4 TEST USED IN THE FIVE STUDIES USED BY EPA

Study	Type of fT4 Assay	Brand	Detection Limit	Interassay Coefficient
Pop *et al.*, 1999	Chemiluminescence	Kodak Amerlite MAB FT4 Assay	8.7 pmol/L	11.1-12.2%
Pop *et al.*, 2003	Chemiluminescence	IMMULITE Free T4	Not given	5.2-20%
Vermiglio *et al.*, 2004	Radioimmunoassay	Amerlex-MAB	Not given	<5%
Finken *et al.*, 2013	Chemiluminescence	Beckman Coulter Access immunoanalyzer	1.9 pmol/L	3.1-5.0%
Korevaar *et al.*, 2016	Chemiluminescence	Vitros ECI; Ortho Clinical Diagnostics	Not given	<5.4%

3.2 Approach 2: BBDR Model Used to Predict Population Shift

Approach 2 uses a population-based approach which estimates the shift in the population of hypothyroxinemic pregnant women that would theoretically result from perchlorate exposure. There is no connection to an adverse effect. Overall, this approach has no reasonable scientific justification.

First, hypothyroxinemia is not an adverse, treatable endpoint. As noted in Section 2.2.2, the ATA and ACOG do not recommend treatment of pregnant women with hypothyroxinemia as there is no demonstrated benefit to doing so.

Second, the choice to define increases in the numbers of hypothyroxinemic women of 1 and 5 % is arbitrary. Since this is not an adverse effect, it is unclear what these values would represent.

3.3 Approach 3: Single Epidemiological Study to Predict fT4 + Neurodevelopment

Approach 3 proposes a two-stage approach as in Approach 1, but uses the relationship presented in a single epidemiological study (Steinmaus *et al.*, 2016) rather than the BBDR model to predict fT4 changes and uses the epidemiological literature to associate hypothyroxinemia with neurodevelopment (uses only Korevaar *et al.* (2016) as the example).

3.3.1 Limitations of the Steinmaus et al. (2016) for use in this manner

The Steinmaus *et al.* (2016) study used a cohort of pregnant women in Southern California (San Diego area) that were part of the Project Baby's Breath Study (a smoking and second hand smoke study). Samples from these women were collected in 2000-2003 and have been in storage. Serum samples were analyzed for TT4, fT4, and TSH and spot urine samples were analyzed for iodine, perchlorate, nitrate, and thiocyanate. The authors reported an association between increasing $\log_{10}$ perchlorate and decreasing fT4 and TT4 and increasing TSH.

One conclusion of the study was stated as:

> Thus, each 10-fold increase in perchlorate was associated with a 0.70-µg/L decrease in T4 and a 0.053-µg/L decrease in fT4, and each 1% increase in perchlorate was associated with a 0.071% increase in TSH.

Although this study contributes to the literature, it is unclear why EPA chose to use this particular study to define the relationship between maternal perchlorate and fT4. There are several concerns with the study design that suggest that this is not the study EPA should use to predict any type of relationship.

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First, the study samples were not collected concurrently. The spot urine samples for perchlorate were collect at a median of 7 weeks of gestation. The serum samples for thyroid hormones were collected at 17 weeks. Perchlorate has a half-life of 6-8 hours. The half-life of fT4 is 5-7 days.

Second, EPA has been clear that its focus is on the first trimester as these are the data that they can link to the neurodevelopmental data. The thyroid hormone data in Steinmaus *et al.* (2016) were collected at a median of 17.1 weeks. This is the second trimester.

Third, one of the interesting results of the study was that the relationship was strongest in women with the highest iodide. One would expect the association would be strongest in low iodide women.

Finally, although the regression produced an intercept which shows the direction of the association (negative or positive) with a 95% confidence interval to demonstrate variability, there are no statistics provided to demonstrate the statistical significance of the regression.

3.3.2 Comparison to BBDR results

As EPA states, the results from Steinmaus give very different values that are not consistent with the BBDR; the dose response of perchlorate on fT4 is much steeper in the epidemiology study compared to the BBDR. EPA notes that the fT4 based on low iodide intake (75 μg/d) is most similar to the lower bound estimate using the equation from Steinmaus *et al.* (2016). The lower bound estimate is based on the upper 95% confidence interval. This is surprising because the urinary iodide levels in Steinmaus *et al.* (2016) were relatively high. The median urinary iodide level is 154.5 and the mean and standard deviation is 214.9 ± 247.3 μg/L. The maximum urinary concentration of iodide was 3,000 μg/L.

Second, this comparison to the lower limit estimate from Steinmaus *et al.* (2016) isn't a comparison to actual data; rather, this is the estimated curve based on the regression of the data.

As discussed earlier, the results of the BBDR model over-predict the effects of exposure to perchlorate based on comparison to several data sets. Approach 3 over-predicts health effect to a greater degree and is not a useful approach.

3.3.3 Equations for deriving change in IQ

EPA uses simple linear equations for calculating change in IQ given a change in fT4. These are based on taking the beta coefficient and the unit change to a change in fT4 (usually some dose of perchlorate compared to no perchlorate). An inherent issue in this methodology is that the perchlorate baseline has a potentially large impact on the overall change. Assuming an equation that calculates the dose of perchlorate that can be applied to result in a 1 point change in IQ, a higher assumed baseline perchlorate allows for a larger amount of perchlorate to be applied (Table 7). Thus, a lower assumed baseline perchlorate will skew the results to a lower final perchlorate concentration.

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TABLE 7 EFFECT OF BASELINE PERCHLORATE ON FINAL PERCHLORATE CONCENTRATION FOR A 1 POINT IQ CHANGE USING THE KOREVAAR MULTIVARIATE MODEL

Baseline perchlorate concentration in urine (µg/L)	Rationale for Baseline Concentration	Baseline perchlorate dose (corresponding to urine) (µg/kg-d)	Perchlorate concentration after exposure (µg/L)	Ratio of baseline to post Urinary Perchlorate (µg/L)	Predicted perchlorate dose after exposure (µg/kg-d)
0.92	At fT4 10th percentile for non-pregnant women of cba in NHANES 2007-12	0.022	147.66	160.5	3.6
3	Median from NHANES 2001-02 cited by Steinmaus	0.073	481.5	160.5	11.7
4.1	Equiv to 0.1 µg/kg-d	0.1	658.05	160.5	16.1
6.5	Median from Steinmaus *et al.* (2016) cohort	0.16	8456.5	1301	206.3
2.25	Mid-point for lowest quartile (<4.5 ug/L), Steinmaus *et al.* (2016)	0.055	3970.35	1764.6	96.8

3.3.4 Comparison to other literature

Most importantly, the results of Steinmaus *et al.* (2016) are in stark contradiction of the rest of the scientific literature evaluating the association between urinary perchlorate and thyroid hormones in pregnant women. Table 8 lists other studies that studied this association with summary data on each. Of these, only the study by Charatcharoenwitthaya *et al. (2014)* reports an association. The results in every other cohort report no association.

Clearly, Steinmaus *et al.* (2016) is contrary to the weight of evidence, uses data collected later than the period of interest during pregnancy, and has study design flaws that preclude its use (i.e., non-concurrent urine and blood sample collection and lack of statistical evaluation of significance).

TABLE 8 STUDIES OF MATERNAL URINARY PERCHLORATE AND SERUM THYROID HORMONES

Study	N	Sample Collection for fT4 (median)	Urinary Iodine (median)	Urinary Perchlorate (median)	Results
Steinmaus *et al.*, 2016	1,476	17.1 +/- 1.5 w 2nd trimester	154.5 sufficient	6.5	Stated association with TT4, fT4, and TSH with perchlorate
Charatcharoenwitthaya *et al.*, 2014	200	9.6 +/- 2 w (mean) 1st trimester	153.5 sufficient	1.9	fT4 and TSH significantly associated with perchlorate
Horton *et al.*, 2015	284	12 +/- 2.8 w 1st trimester	138.5 marginally deficient	2.57	No associations reported
Mortensen *et al.*, 2016 (NCS cohort)	329	3rd trimester	Not given	4.0	No associations reported
Mortensen *et al.*, 2016 (NHANES cohort)	533	1st, 2nd, and 3rd trimester	Not given	3.3	No associations reported
Pearce *et al.*, 2010 (Cardiff hypo-thy/thyrox cohort)	374	12.5 (12.8 +/- 1.6 given in Lazarus *et al.*, 2003)	98	2.1	No associations reported
Pearce *et al.*, 2010 (Cardiff euthyroid cohort)	480	12.8 +/- 1.6 1st and 2nd trimester	117	2.6	No associations reported
Pearce *et al.*, 2010 (Turin hypo-thy/thyrox cohort)	261	12.8 +/- 1.6 1st and 2nd trimester	55	5.04	No associations reported
Pearce *et al.*, 2010 (Turin euthyroid cohort)	526	12.8 +/- 1.6 1st and 2nd trimester	50	5.2	No associations reported
Pearce *et al.*, 2011 (LA cohort)	134	9.1 +/- 2 1st trimester	144	7.8	No associations reported
Pearce *et al.*, 2011 (Argentina cohort)	107	10.0 +/- 2 1st trimester	130	13.5	No associations reported
Pearce *et al.*, 2012	134	10.9 +/- 2.3 1st trimester	120 marginally deficient	4.1	No associations reported

4.0 OTHER ISSUES

In Chapter 8 of its Draft Report, EPA lists other endpoints that may have a connection with perchlorate. Largely, these are unfounded and not supported by the literature.

4.1 Heart Disease

EPA reports that hypothyroidism is associated with heart and vascular disease. The MOA for perchlorate notes that hypothyroidism is the first hypothesized adverse effect due to perchlorate exposure (NRC, 2005). Although this has never been demonstrated in humans, no alternative to the MOA has been supported by the literature. Cardiovascular disease is associated with hypothyroidism, but is further down the continuum of effects. It is not a more sensitive endpoint than the recognized adverse effect of hypothyroidism or the first measureable effect of IUI.

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4.2 Comparative Toxicogenomics Database

EPA cites the Comparative Toxciogenomics Database as suggestive of "455 diseases potentially associated with perchlorate" and "mechanistic correlations have been reported for perchlorate exposure and thyroid diseases such as goiter and hypothyroidism, as well as necrosis, hypertrophy, and jaw abnormalities". EPA further states "Adverse health outcomes based on these alterations range from neurodegenerative disease to cancer."

The CTD is a large, hand-curated, integrative database with information on gene regulation, chemical exposures, and disease processes. It deliberately includes data from many different species, exposure protocols, and analytical techniques as it is intended to drive hypotheses. A study may report a gene up- or down-regulated in response to perchlorate (in any organism and at any dose). This gene may also be associated with disease processes or biological pathways that have not been reported to occur with perchlorate, but are associated with the gene change.

When querying "perchlorate," there are 158 genes changes, the two most common being SLC5A5 (the gene coding for the NIS protein) and TSHB (the gene coding for the TSH beta protein). Further, there are 487 diseases and 72 pathways. These diseases and pathways have largely not been demonstrated with perchlorate and are theoretical.

The studies the gene regulation are based on are not relevant to human exposures (e.g., high doses, animal models, exposure routes) and have inconsistent results (e.g., TSH both up and down regulated). Any disease or pathway associated with those genes are used to make the association. The CTD's intended use is viewing these relationships and forming hypotheses; then, the researcher can design studies to test these hypotheses. However, EPA's use of the CTD in a regulatory document is inappropriate and misleading.

5.0 OTHER GOITROGENS

Other chemicals have the same MOA as perchlorate and are found at levels in the diet that are greater than perchlorate, namely nitrate and thiocyanate. Cumulative risk assessment is commonly used by EPA when evaluating pesticides, but has not been applied under the SDWA. The total effect on IUI can be estimated using perchlorate equivalence. The equivalence is based on affinity of the anion to the symporter. The study to determine equivalence has been conducted in cell culture using human NIS transfected into the cells (Tonacchera *et al.*, 2004). This is a reliable method that has been used for decades in medical pharmacology. Although some criticize cell culture as a substitute for human studies generally, in this case, the relative interaction between the anion and the receptor is better quantified *in vitro*. Additionally, multiple animal studies have reported similar potencies of the three goitrogens (Wyngaarden *et al.*, 1952; Wyngaarden *et al.*, 1953). Willemin and Lumen (2016) also published the development of a PBPK model to evaluate the dose-response of thiocyanate; thus, it is possible to increase the utility of the Model by introducing nitrate and thiocyanate.

OIG released a report in 2010 recommending and demonstrating use of cumulative risk assessment for perchlorate, nitrate, and thiocyanate. OIG also included iodine deficiency as a thyroid stressor. The report noted that perchlorate accounted for less than 1% of total goitrogen load on the thyroid and regulation of this chemical in isolation would produce no benefit to public health. Other studies have also reported the same contribution of perchlorate to total goitrogen load (Tarone *et al.*, 2010; Bruce *et al.*, 2013).

Relatedly, the studies used to calibrate the model did not consider background doses of goitrogens. Only two studies were used to calibrate infant perchlorate, TT4, and fT4: Cao *et al.* (2010) and Leung *et al.* (2012). Cao *et al.* (2010) measured infant urinary nitrate, thiocyanate, and perchlorate, and reported geometric means and 95% confidence intervals for urinary nitrate of 95 μg/g creatinine (69-131) and urinary thiocyanate of 1000 μg/g creatinine (760-1320). In Leung *et al.* (2012), perchlorate, thiocyanate, and iodine were measured. For thiocyanate, they report thiocyanate levels of 373.5 μg/L (31.1–2420 μg/L) in maternal urine, and 193 μg/L (21.7–1880 μg/L) in infant urine (Leung *et al.*, 2012). The range that these two studies report spans two orders of magnitude suggesting significant variability in this study population. As a point of reference, NHANES 2011-2012 reports a geometric mean urinary thiocyanate and 95% confidence interval of 1133.5 μg/L (1002.1–1282.2) for females age 20 and older (Jain, 2016).

EPA does not include the other goitrogens in the model. Rather the Agency assumes that exposures are accounted for in the calibration populations.

> Since data used in the calibration of the BBDR model were taken from NHANES 2007-12, with exclusion only for frank thyroid disease or medical treatment, they are presumed to be representative of the U.S. population as a whole. Since the NHANES data are also used to estimate overall exposure of the U.S. population to other goitrogens, the degree to which these may not reflect actual population exposure would point to an underlying problem in the NHANES sampling. The use of these data in calibration of baseline thyroid hormone status effectively means that the predicted perchlorate dose-response is additive to the effect of existing exposure to other goitrogens in the NHANES 2007-12 population.

Thus, EPA's calibration based on studies where the impact of other chemicals with the same MOA also may be contributing to data reported is neither described as a limitation, nor considered in the assessment.

6.0 CONCLUSIONS

On September 15, 2017, EPA published a notice announcing the release of five documents, which taken together, provide the scientific basis to inform EPA's development of an MCLG.

We provided comments on the overarching topics of the revised BBDR model, hypothyroxinemia as an endpoint, and the derived association with neurodevelopment. We then discussed EPA's three approaches to inform the MCLG. Finally, we discussed other health endpoints that EPA mentions and the concurrent exposures to other goitrogens.

Regarding the overarching topics, we point out critical scientific issues.

BBDR model: EPA's revision has increased the ability of the model to accurately predict thyroid hormone in first trimester pregnant women, but the model continues to over-predict health effects for a given perchlorate exposure. To further the model for use in informing the MCLG, EPA should increase transparency, demonstrate validity with iodine deficiency in pregnancy, and provide a clear representation of limitations of the model. If EPA intends to use the output of the model to represent an average or median individual, the model parameters must also be chosen from the central point of the distribution. For example, modeling a weak TSH responder was a policy decision that results in a conservative output.

Hypothyroxinemia: Authoritative bodies such as the ATA and ACOG do not recommend treatment for hypothyroxinemia in pregnancy. The literature associating hypothyroxinemia and

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neurodevelopmental outcomes is not sufficiently robust to support a mathematical prediction. There is no study that reports that perchlorate causes hypothyroxinemia. There is no study that suggest that hypothyroxinemia is an intermediate step prior to hypothyroidism. EPA should consider using the accepted NRC MOA with hypothyroidism as the first adverse effect.

Neurodevelopment: The Agency is using multiple endpoints and those that are controversial from a scientific standpoint. The types of studies used are were developed to identify individuals who may require specialized learning programs due to clear disability. EPA focused on only five studies that were chosen because they reported a significant effect to the exclusion of all others. These five studies may not be applicable to the US populations and the associations are based on neurodevelopmental tests that lack sensitivity and specificity to detect small differences.

The three approaches are all limited by at least one of the above issues. Although we believe a revised BBDR model can inform the process, the use of hypothyroxinemia and neurodevelopment should not be used as EPA has proposed. The first two approaches use the BBDR model and either the epidemiological literature on neurodevelopment (Approach 1) or a theoretical population shift in hypothyroxinemic pregnant women (Approach 2). The second approach could be viable if the endpoint addressed were hypothyroidism rather than hypothyroxinemia, given the ATA's clinical position and the NRC MOA.

It is unclear if EPA intended the third approach to be a legitimate option as it is described only in the Appendix. Approach 3 proposes a two-stage approach as in Approach 1, but uses the relationship presented in a single epidemiological study (Steinmaus *et al.*, 2016) rather than the BBDR model to predict fT4 changes and uses the epidemiological literature to associate hypothyroxinemia with neurodevelopment (using only Korevaar *et al.* (2016) as an example). This study has critical flaws that preclude its use in the manner EPA proposes. The data from Steinmaus *et al.* (2016) overpredict fT4 levels to an even greater extent than the BBDR model. Approach 3 focuses on a single study to derive a correlation and disregards a large body of studies that shows no adverse health impacts at environmental levels of exposure.

In conclusion, we provided recommendations for the Agency that will improve the work they have conducted to this point in time. We appreciate the magnitude of work that EPA has conducted with the time constraints imposed by the Consent Decree to implement the improvements we see in the revised BBDR model. We believe that public health is best served with a rigorous scientific review. We appreciate that the Agency has such clear guidelines (*Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (EPA, 2002)). We encourage the Agency and the Peer Reviewers to use this guidance as it provides a sound scientific approach to making important decisions on data quality for health assessments.

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APPENDIX A

INTERTOX LETTER TO VERSAR, INC. REGARDING DRAFT CHARGE QUESTIONS, OCTOBER 6, 2017

INTERTOX

600 Stewart St.
Suite 1101
Seattle, WA 98101 Tel 206.443.2115
U.S.A. Fax 206.443.2117

October 6, 2017

Versar, Inc.
6850 Versar Center
Springfield, VA 22151T
Delivered by email: perchlorate@versar.com

RE: PERCHLORATE PEER REVIEW

Dear Sir or Madame,

In response to the Federal Register Notice [EPA–HQ–OW–2016–0439; FRL–9967–70–OW] and on behalf of the Perchlorate Study Group (PSG),[1] Intertox is pleased to submit comments regarding EPA's *Draft Peer Review Charge Questions* on its *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*. The EPA's charge questions can be found here.

We provide comments in this letter to the Agency. We outline overarching concerns with the document, we request that EPA provide essential documents to the peer reviewers, and we comment on the questions themselves. The Agency is releasing an updated BBDR model as well as three (not two) new proposed methods to derive an MCLG. It is an unrealistic expectation of the Agency to have volunteer experts provide input on important scientific issues without adequate time, transparency, guidance, and precise questions. We are concerned that the Agency will receive a peer review that lacks quality, consistency, and a viable path forward for EPA to improve. We submit these comments in the spirit of assisting and supporting the Agency in its mission to use the best science to determine an MCLG for perchlorate.

Overarching concerns with the Agency's document

There are four major issues related to the Peer Review process:

1) Inadequate time to review the documentation jeopardizes the quality of the peer review process
2) No clear process to critically review the updated BBDR model based on the criticisms of the first peer review panel
3) The manner in which the questions are written is inconsistent with the Agency's own Peer Review Handbook and cannot provide the quality of scientific information needed
4) Omission of questions on specific subjects casts the transparency of the process into doubt and must be addressed with additional questions

First, the Agency has set up a Herculean task for the peer reviewers: a critical review of more than 500 pages of dense scientific documentation by October 30, 2017 (45 days from when the draft report was published). With this timeframe the Agency places an undue burden on volunteer experts—they simply will not have the time to adequately digest the contents of this work given the

[1] *The Perchlorate Study Group is supported by Aerojet Rocketdyne, American Pacific Corporation, Lockheed Martin and Orbital-ATK. These companies have worked cooperatively with the U.S. Environmental Protection Agency to increase scientific and medical understanding of perchlorate's risk to human health.*

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multidisciplinary nature of the work the Agency is proposing. Therefore, the Agency reduces the strength of the peer review process and the scientific credibility it would impart.

Second, we are delighted that the Agency has listened to the first Peer Review and has updated its BBDR model on several critical issues. However, the BBDR model has changed significantly and thus needs a complete evaluation by scientists with experience, training, and knowledge and the ability to focus on the BBDR model rather than review the BBDR and all the additional material related to the MCLG approaches. Relatedly, the current EPA document fails to transparently discuss the criticisms of the first peer review panel. The Agency must make clear what the issues were rather than asking peer reviewers to read another technically dense document.

Third, the questions in EPA's document are not clear or precisely written. According to the Agency's handbook on peer review (4th edition of the Peer Review Handbook), there are two types of questions necessary for an adequate peer review. The first identifies broad scientific issues on which the Agency would like feedback. There are only two questions that EPA lists under "General Questions" for the reviewers to answer. The remainder are all highly technical, requiring expertise in PBPK modeling, maternal endocrinology, cognitive sciences, and epidemiology. All questions need to be rewritten for the Agency to obtain the quality of scientific information it seeks.

Fourth, there is a clear issue of transparency in the omission of questions on the third approach the Agency is proposing to derive an MCLG. Using Steinmaus *et al.* (2016) to derive the MCLG is an additional approach. The documents need to be rewritten to address this point. We provide specific examples of questions that address this topic below.

Documents EPA must provide to peer reviewers

The Agency must add additional resources to support peer reviewers with their tasks. The database of perchlorate literature is robust, replete with high-quality scientific studies conducted over 60 years. The Agency must provide the authoritative reviews by the National Research Council and ATSDR's Toxicology Profile for perchlorate. These documents will provide the reviewers with the foundational scientific information on the toxicology and pharmacology of perchlorate, which is essential to a rigorous evaluation of perchlorate.

Given the Agency's requirement for high quality information, peer reviewers should be directed to, and required to read, the Agency's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*.[2] It would help the peer reviewers to understand the importance of data quality, and how the Agency reviews its scientific information.

Comments on Specific Questions in the Document

General Questions

These need increased clarity. The Agency will not receive quality information when it asks peer reviewers to "comment on the appropriateness." The questions lack specificity, generally requesting the reviewers to "provide comments" rather than asking specific questions. There are many examples of these ambiguous phrases throughout the charge questions. Such undefined requirements for answering a question make it difficult for any peer reviewer to provide a consistent and thorough assessment. The Agency must provide clear and directed questions that are critical to understanding the goal and limitations in determining whether to set or not set an MCLG.

[2] https://www.epa.gov/sites/production/files/2015-08/documents/epa-info-quality-guidelines.pdf

Specifically, the questions need to be rewritten to be more directive in obtaining the information the Agency needs.

Additionally, more broad questions are required. We suggest additional general questions below to support the peer reviewers in providing constructive feedback to the Agency, taking into account the context, background science and possible limitations of what they are being asked to do.

1) Several human studies specifically evaluate a nonadverse and precursor event to thyroid hormone changes. The most conservative No Observable Effect Level (NOEL) for IUI is 7 μg/kg-d (Greer et al., 2002). Importantly, no other effects (i.e., changes in thyroid hormone) occur unless IUI occurs first. The BBDR model predicts changes in thyroid hormones without changes in IUI. How should EPA reconcile the clinical data with the BBDR results?

2) Given the inherent conservatism of the BBDR model output (fT4) to population shifts of hypothyroxinemia and possible cognitive changes, does the literature support this mechanism of action and the predicted effects (perchlorate exposures causing isolated maternal hypothyroxinemia leading to permanent cognitive changes in offspring)? EPA uses only five population studies that demonstrate cognitive outcomes. Is this scientifically defensible? Should negative studies and/or additional clinical be used in the assessment?

3) The EPA SAB in 2012 recommended that the Agency use hypothyroxinemia as an endpoint. The Agency is concerned that there were no clinicians on the panel to aid the Board in making that determination. Clinicians were requested to participate in the first peer review and stated that hypothyroxinemia is not a clinically defined or treatable disease, whereas hypothyroidism is. Is the Agency still required to use hypothyroxinemia rather than hypothyroidism, an adverse effect, as the endpoint of concern?

4) The updated BBDR model incorporates changes to its first released model. The Scientific protocol would require this model be peer reviewed again. Has the Agency provide sufficient time, resources, expertise, and evaluation of this revised model? What expertise in this peer review group is used to make this assessment? Did any of the peer reviewers have the time, equipment, and resources to build and run the model? Did any of the peer reviewers ask EPA to run scenarios for them? What is the clear recommendation of the peer review on how to use this model?

5) The Agency uses conservatism in its approach to determining acceptable exposures for the US population. The purpose is to err on the side of not underpredicting a possible health effect. To derive an MCLG for perchlorate, EPA is engaging new methods to set acceptable levels of chemicals, and each method is conservative. If using a BBDR model has built-in conservatism, the translation to fT4 to clinical significance is conservative, and the approach to determining cognitive effects is conservative, how accurate is this new method, and is it realistic in predicting adverse outcomes?

6) The Agency is interested in assessing neurodevelopmental effects of chemical agents. However, neurodevelopmental effects cover a broad range of effects from motor, cognitive, reaction time, behavioral, and many others. For this assessment, we are using several neurodevelopmental endpoints. Given that, are all neurodevelopmental endpoints relevant or are some more important than others? The tools used to test for these developmental parameters are rather specific to a certain age and population, so, is it appropriate to use any specific age group as the metric? If a tool is useful for a given age and inadequate for prediction of long-term effects should it be used? If there is a statistically significant effect

(e.g., IQ point difference of 2 points) and the standard error of the test is +/- 10 points, is this an important outcome?

The lack of broad questions raises a concern over transparency. It is not in the Agency's best interest to focus peer reviewers on a small portion of a robust database when the Agency needs a strong scientific rationale for deciding whether it should set an MCLG for perchlorate.

Technical and Specific Questions

As noted above, the amount of material to critically review and provide the Agency with comments on by October 6th cannot possibly be given adequate consideration or the required scientific vigor, . This is particularly the case for the technical questions. The lack of adequate time should give the Agency pause to ask itself if it is getting the quality it needs.

Parallel to our observations about the ambiguity of language for broad questions, the same improvement to issues in the technical section is needed. Peer reviewers need clear and concise questions so that they can help the Agency. As currently written, the technical questions allow the Agency to disregard the question if misinterpreted, for example. Unclearly written questions waste a valuable opportunity to obtain critical feedback that will be used to support EPA's final MCLG.

We are concerned about the lack of questions regarding the use of Steinmaus et al. (2016) to define the change in fT4 levels. Using Steinmaus et al. (2016) adds a third approach to calculating an MCLG. The lack of Charge Questions for this third approach is puzzling. We submit potential questions below for consideration and request that the Agency provide more questions to guide the peer reviewers on this approach. The scientific validity of this approach <u>must</u> be assessed.

1) In its 2013 report, the SAB found that the 13 epidemiological studies that had been published since 2005 were "*insufficient to guide causal inference with regard to the association between perchlorate exposure and thyroid dysfunction*."

   In Appendix B of its report, the SAB identified important limitations of these epidemiological studies. In Appendix C of the Peer Review Draft, EPA uses two epidemiological studies (Steinmaus et al. (2016) and Korevaar et al. (2016)) to create a quantitative estimate between perchlorate exposure and change in IQ.

   > Do the studies used in Appendix C have similar limitations in determining causal inference as the ones the SAB listed in Appendix B of the SAB report? Is EPA's use of the epidemiology studies in Appendix C consistent with the advice provided by the SAB?
   >
   > Do these two studies avoid the problems of confounding, other goitrogen exposure, and limitations of spot urine sampling the SAB identified in Appendix B of the SAB report?
   >
   > Is the use of these two studies in isolation and the absence of other studies (to gather the weight-of-evidence) scientifically defensible? Please list and comment on other studies would have been relevant.

2) The estimated thyroid hormone changes in Steinmaus (2016) differ from the results of the BBDR model by a substantial margin.

   Does the report adequately explain the reasons for the differences? If not, what are the scientifically-justified reasons? What are the potential confounders in Steinmaus et al. (2016)?

   Is EPA's use of the perchlorate concentration at the 10th percentile fT4 level justified as a baseline perchlorate concentration? What are other approaches for defining a quantitative value of "baseline?"

   The assumption of baseline perchlorate has a profound effect on change in fT4. Does EPA adequately justify the use of its value as opposed to a mid-distribution value or some other point on the distribution? Should this value by tied to fT4?

   Based on the weight-of-evidence, which approach (BBDR or results of Steinmaus et al. (2016)) is a better approximation of the U.S. population fT4 and sensitive sub-population fT4?

3) In Appendix C of the Peer Review Draft, EPA uses one of the five relationships used in the main report to relate the Steinmaus (2016) change in fT4 to changes in IQ.

   Please list and comment on the scientific merits and limitations of selecting the Korevaar (2016) study for this relationship.

   The study populations in the two studies (Steinmaus and Korevaar) are different (e.g., ethnically, socioeconomically, nutritionally). Did the analysis in Appendix C adequately control for these differences?

   The analysis conducts a partial Monte-Carlo analysis of variability of the two effect estimates. Does this approach fully characterize the uncertainty in the quantified estimates in Appendix C?

   Tables C-6 through C-8 show that at least a 13% reduction in fT4 is required to lead to a change in one IQ point. These results do not account for homeostasis and the TSH-moderated feedback loop that would increase the production of thyroid hormones as in the BBDR model. Please comment on the scientific basis of this approach.

Thank you for the opportunity to provide these comments. Intertox continues to read the EPA documents and will provide more specific comments to EPA as soon as it is able.

Sincerely,

Richard C. Pleus, PhD, MS
Intertox, Inc.

October 6, 2017

APPENDIX B

INTERTOX LETTER TO VERSAR, INC. REGARDING INTERIM LIST OF PEER REVIEWERS, OCTOBER 6, 2017

INTERTOX

600 Stewart St.
Suite 1101
Seattle, WA 98101 Tel 206.443.2115
U.S.A. Fax 206.443.2117

October 6, 2017

Versar, Inc.
6850 Versar Center
Springfield, VA 22151T
Delivered by email: perchlorate@versar.com

RE: PERCHLORATE PEER REVIEW

Dear Sir or Madame,

In response to the Federal Register Notice [82 FR 43362 (September 15, 2017)] and on behalf of the Perchlorate Study Group (PSG)[1], Intertox is pleased to submit comments regarding the Interim List of Peer Reviewers. The PSG is committed to assisting the Environmental Protection Agency (hereafter EPA or the Agency), as the PSG has for more than 16 years, to ensure that the information it disseminates adheres to the basic standards of quality, objectivity, utility, and integrity. It is in this spirit that Intertox provides comments on the interim list of peer reviewers.

The Agency has released an updated BBDR model as well as three (not two) new proposed approaches to derive an MCLG. It is unrealistic of the Agency to release more than 500 pages of technical documentation and expect to receive constructive comments on the main document and appendices, the updated BBDR model, comments on Charge Questions, and the Interim Peer Review Panel. The Agency has presented groundbreaking and highly influential science and it deserves thoughtful response.

Based on a review of the documents provided by EPA, additional disciplines are required which are not represented by the scientists listed on the Interim List. These must be included for a meaningful review:

- Developmental psychologists - experts in childhood development; expertise in instruments (e.g., IQ tests) to predict adult outcomes from studies in children
- Clinical psychologists - experts in the use and administration of cognitive testing
- Receptor pharmacologists - experts in the understanding of the physiology of receptors (e.g., endocrine receptors)
- Thyroid endocrinologists with expertise in neurodevelopment - expertise in endocrinology with a subspecialty in neurodevelopment
- Statistician in population studies - expertise in how to apply hormonal outcomes to populations

The first peer review benefited from having clinicians empaneled to address key issues of relevance and significance of thyroid hormone values and clinical outcomes. These issues will be just as key

[1] *The Perchlorate Study Group is supported by Aerojet Rocketdyne, American Pacific Corporation, Lockheed Martin, and Orbital-ATK. These companies have worked cooperatively with the U.S. Environmental Protection Agency to increase scientific and medical understanding of perchlorate's risk to human health.*

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for the present peer review process and the clinicians should be included in the second peer review. Furthermore, with the evaluation of the revised BBDR model, expertise in modeling is required in this second peer review; thus, the BBDR modelers should also be included.

Thank you.

Sincerely,

Richard C. Pleus, PhD
Intertox, Inc.

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The US Conference of Mayors

November 17, 2017

Mr. Michael H. Shapiro
Acting Assistant Administrator
Office of Water
US Environmental Protection Agency
Washington, DC

RE: Comments on EPA's Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate - Docket ID No. EPA-HQ-OW-2016-0438, (82 Fed. Reg. 43354, Sept. 15, 2017). http://www.regulations.gov

Dear Mr. Shapiro:
The United States Conference of Mayors (USCM) appreciates the opportunity to provide comments to the U.S. Environmental Protection Agency (EPA) regarding the "**Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate".** USCM has followed the development of this rule for a number of years because it impacts our member cities who provide drinking water in their communities.

The USCM commends EPA for developing the revised "Biologically Based Dose-Response (BBDR) Model"; and, development of several Approaches to Inform the Derivation of a Perchlorate MCLG". While these models are intended to derive a limit and a goal for perchlorate we are concerned about the multiplicity of model uncertainties, and the lack of replicated studies to support a limit. We request that EPA make fully transparent the magnitude of uncertainty these models present, and how the panel dealt with them in combination.

Local government is the primary provider of municipal drinking water in the United States, spending over $65 billion on services and infrastructure. Our citizens and customers are also facing water service affordability issues in every community. Any new primary drinking water standard will require rate increases, and thus we urge EPA to weigh the level of uncertainty in the models supporting the rulemaking against the cost of compliance.

USCM appreciates consideration of these comments by EPA and peer review panel. If you have any questions, please feel free to contact Rich Anderson (randerson@usmayors.org) or Judy Sheahan (jsheahan@usmayors.org) of my staff.

Sincerely,

Tom Cochran
CEO and Executive Director
The US Conference of Mayors

Western Growers

WESTERN GROWERS®

Fresh produce from our families to yours

November 20, 2017

Michael Shapiro
USEPA Headquarters
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460

Re: Docket ID No. EPA-HQ-OW-2016-0438-0017: Requests for Comments: Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate

Western Growers is a non-profit trade organization that represents California, Arizona, Colorado and New Mexico based growers and handlers of fresh fruits nuts and vegetables. Our members produce and sell over half of the total US fresh produce including both conventional and organic crops. Over the years Western Growers has provided commentary to USEPA and others regarding lower regulatory limits for perchlorate because of our concerns for potential adverse impacts to growers including increased water costs and perceptions about the safety of foods that may contain traces of perchlorate and other thyroid inhibiting compounds.

Western Growers appreciates the opportunity to provide brief comments on the BBDR documentation and model as USEPA strives to assure scientific rigor of the model development and validation. The decisions that are made by USEPA during this development period have a direct bearing on not only the water providers but also many water users including growers in the West.

Among our key concerns is the identification of the appropriate endpoint. Western Growers has long contended that transient thyroid hormone changes are not adverse in and of themselves. It is our understanding that hypothyroidism is the first adverse effect (NAS 2005) and that there are several non-adverse precursors to the first adverse effect, including inhibition of iodide uptake in the thyroid, which is the first measurable effect in the body. It seems that USEPA is contemplating the use of hypothyroxinemia, which is not an adverse effect, and Western Growers asks that the rationale for this decision and its departure from the National Academy be clearly articulated as USEPA moves forward.

If the MCLG is established on the basis of an effect that occurs upstream of the identified first adverse effect, and that effect is transient as well as heavily influenced by many factors other than simple exposure to perchlorate, it could set a problematic precedent for future regulatory decisions. The agricultural industry is certain to be impacted by the USEPAs decision making on perchlorate. Western Growers urges the USEPA to take a realistic approach to their modeling efforts beginning with the selection of appropriate critical effects.

Respectfully,

Senior Vice President
Western Growers
Irvine CA

Public Comment Summary Report for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water

EPA Contract No. EP-C-13-010
Task Order No. 2015-022

December 16, 2016

Prepared for:
U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water
Standards and Risk Management Division
1200 Pennsylvania Avenue, NW (MC 4304T)
Washington DC 20460

Prepared by:
Versar, Inc.
6850 Versar Center
Springfield, VA 22151

I. INTRODUCTION

Versar, Inc. (Versar) is an EPA contractor charged with coordinating the external peer review of EPA's Draft Biologically Based Dose-Response (BBDR) model and a draft BBDR model report entitled "Biologically Based Dose-Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses." As part of the peer review process, EPA published a Federal Register Notice (81 FR 67350) on September 30, 2016 to announce a public comment period. The original 45-day public comment period ended on November 14, 2016, but the public comment period was extended until November 25, 2016. Supporting documentation, including the charge questions that will be addressed by the peer reviewers, was also made publicly available.

The purpose of this document is to provide a brief overview of the public comments submitted to EPA's public docket (Docket ID No. EPA-HQ-OW-2016-0438) by the published deadline of November 25, 2016. The public comments in their entirety are included with this report (Attachment 1) and are also available for download from the Federal docket (*http://www.regulations.gov*).

II. PUBLIC COMMENT OVERVIEW

A total of 10 comments/submissions on were uploaded to the docket, however, only nine of these submissions contained technical comments on the BBDR model and report, as one submission (from the Perchlorate Study Group) was a request for an extension to the public comment period.

The following nine organizations/individuals submitted technical comments:

- Department of Defense
- Izze Kraiman, West Chester University
- The Chlorine Institute
- American Chemistry Council
- American Water Works Association
- Environmental Defense Fund/Natural Resources Defense Council
- Intertox, Inc. (prepared for Perchlorate Study Group)
- Gradient
- NASA

Table 1 below provides a list the comments submitted, the number of pages for each, the technical author (if provided), and a list of topics covered. Overall, the comments discussed EPA's choice of hypothyroxynemia as the critical effect, the lack of data or limited data for model parameterization and validation, compensatory (homeostatic) control mechanisms, and chemicals with the same mechanism of action as perchlorate, among other topics. Some of the submitted comments pertain to the maximum contaminant level goal (MCLG), and therefore are not applicable to this peer review meeting. A second peer review will be held in the future on a report that evaluates methods to apply the final BBDR model to develop a MCLG for perchlorate in drinking water.

Public Comments Submitted to Docket EPA-HQ-OW-2016-0438				
Submitter Organization	Technical Author	No. of Pages	Topics covered	Notes
1. Department of Defense	Not provided	10	• HPT feedback system • Binding assumptions for thyroid hormones • Maternal fT4 during pregnancy and neurodevelopmental effects • Statistical definition of hypothyroxynemia and adverse outcomes at lifestages considered • Literature search for BBDR model • Clarification of data review process for model calibration • Discussion and documentation of model calibration process • Model calibration results and summary of calibration results • Dose-response evaluation • Local sensitivity analysis of BBDR model with perchlorate • Three-compartmental thyroid • 'Normal adult' urinary clearance parameter for lactating mother	Twenty specific comments with suggested actions organized by categories: 11 science comments classified as major, 8 science comments not classified as major, and 1 editorial comment.
2. Izze Kraiman, West Chester University	--	8	• Proposed maximum contaminant level (MCL)	Document discusses studies that support the proposed MCL of 0. 7 µg/day.
3. The Chlorine Institute	Not provided	4 + 31 page ENVIRON study	• Lack of data or limited data for the life-stage human values • Aggregate and cumulative exposures to chemicals with the same mode of action to perchlorate • Lack of appropriate data to validate the method • Homeostatic control mechanism • Additional resources to be reviewed and considered in proposed BBDR model	The commenter provided an evaluation conducted by ENVIRON International Corporation on the health advisories and standards for perchlorate levels in drinking water.

Public Comments Submitted to Docket EPA-HQ-OW-2016-0438				
Submitter Organization	**Technical Author**	**No. of Pages**	**Topics covered**	**Notes**
4. American Chemistry Council	Not provided	5	• Use of sensitive (nutritionally iodine-deficient) subpopulations for BBDR modeling and uncertainty factors in derivation of an MCLG • Hypothyroxinemia and the critical effect • Lack of appropriate data for model parameterization and validation	
5. American Water Works Association	Michael Dourson, Ph.D., DABT, ATS; John Reichard, Ph.D., Pharm D. Toxicology Excellence for Risk Assessment (TERA) Center University of Cincinnati College of Medicine	21	• Hypothyroxinemia and the critical effect • Up regulation of the production of thyroid sodium-iodine symporter proteins • Use of sensitive (nutritionally iodine-deficient) subpopulations for BBDR modeling and uncertainty factors in derivation of an MCLG • Deviations between the model output and observations from prospective epidemiology studies • Clinical relevance of the breast-feeding maternal population	The commenter provided a report prepared by TERA. The report also discusses recommended changes to the charge questions.

6. Intertox, Inc	Not provided	33	• Improvements to the draft model report (Section 3.0)
			• Improvements to the draft BBDR model (Section 4.0)
			• Overarching concerns with both the model and report (Section 5.0) including:
			  ○ Hypothyroxinemia and the critical effect
			  ○ Goitrogens with the same mechanism of action as perchlorate
			  ○ Compensatory mechanisms, such as TSH feedback or increase in NIS activity
			  ○ Animal data on neurodevelopmental outcomes
			  ○ Inconsistency of model predictions with the known MOA
				Document prepared by Intertox for the Perchlorate Study Group.

Public Comments Submitted to Docket EPA-HQ-OW-2016-0438				
Submitter Organization	**Technical Author**	**No. of Pages**	**Topics covered**	**Notes**
7. Environmental Defense Fund/ Natural Resources Defense Council	Not provided	7	• Expansion of the model to include the first two trimesters of pregnancy • Use of a range of iodide levels (95th and 99th percentiles of pregnant women) in the model • Co-exposures to thiocyanate and nitrates (as well as other thyroid hormone disruptors)	--
8. Gradient	Not provided	7	• Potential impacts of thiocyanate (SCN) and nitrate (NO3) on the thyroid and thyroid hormone synthesis. • Other mechanisms of iodine transfer into breast milk • Possible compensation/adaptation in response to hypothyroxinemia • Early stages of gestation not addressed in the model • Use of probabilistic models • Interpretation of Aboul-Khair *et al.* publication on thyroid function during pregnancy • Clarification of what's considered adverse • Transparency in model validation and precision • Model predictions vs actual data • Changes in NIS inhibiting potency • Modeling of earlier time points (first few days of life)	The document also discusses issues related to clarity of the text or need for additional discussion.
9. NASA	Not provided	3	• Hypothyroxinemia as the end point • Documentation on method calibration • Independent evaluation and validation of the model • Support for model assumptions (including consideration of sensitivity, lack of application to the developing fetus, assumptions on the nature and impacts of Perchlorate exposure in specific subpopulations, and rates of urinary clearance)	--
10. Perchlorate Study Group	Not applicable	2	Not applicable	Request for an extension to the public comment period

Attachment 1

Public Comments

Public Comments

Submitted By

Department of Defense

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
3400 DEFENSE PENTAGON
WASHINGTON, DC 20301-3400

ENERGY,
INSTALLATIONS,
AND ENVIRONMENT

NOV 1 8 2016

Mr. Joel Beauvis
Deputy Assistant Administrator
Office of Water
U.S. Environmental Protection Agency
Mail Code 4101
1200 Pennsylvania Ave. N.W.
Washington, DC 20460

RE: Department of Defense Peer Review of Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate (EPA Docket ID No. EPA-HQ-OW-2016-0438, September 30, 2016)

Dear Mr. Beauvis:

Enclosed please find the Department of Defense technical comments related to the draft "Biologically Based Dose-Response Model" that will be used in decision making for the perchlorate national primary drinking water regulations.

Sincerely,

Maureen Sullivan
Deputy Assistant Secretary of Defense
(Environment, Safety, and Occupational Health)

Enclosure:
As stated

Department of Defense Comments on Public Review EPA BBDR Model Document

11/18/16

Comments submitted by: OASD(EI&E), ESOH Directorate, CMRM Program	Organization: Department of Defense	Date: 11/18/2016

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major (M) i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	General	All	A major limitation on the use of these models is the lack of incorporation of the hypothalamic pituitary thyroid (HPT) axis in the models, this limits their ability to focus on the underlying mechanisms that are disrupted by perchlorate. Use of models that are restricted to operating at levels of perchlorate and iodine intake where thyroid homeostasis is expected to be auto-regulated ignores sensitive subpopulations, such as already hypothyroid pregnant women and fetuses. A robust model should predict kinetics and sometimes responses over a large range of doses; this can often help ensure that predictions are mechanistically based rather than simply empirical. Further the use of the model for other thyroid disruptors is restricted without the inclusion of the HPT axis.	There is available tracer data (both radioiodide and thyroid hormones), as well as existing thyroid hormone models (DiStefano et al., 1982; Eisenberg et al., 2010) in the literature that could be incorporated into the model structure. Please consider expanding the iodide model to include the HPT feedback system. This would expand the applicability of the model for addressing similar anions that exist at higher concentrations in the environment than perchlorate as well as future contaminants that may disrupt thyroid function. DiStefano JJ 3rd, Malone TK, Jang M. 1982. Comprehensive kinetics of thyroxine distribution and metabolism in blood and tissue pools of the rat from only six blood samples: dominance of large, slowly exchanging tissue pools. Endocrinology. 1982 111(1):108-17. Eisenberg M, Samuels M, DiStefano JJ III. 2008.	S/M

ED_005043_00062728-00009

				Extensions, validation, and clinical applications of a feedback control system simulator of the hypothalamo-pituitary-thyroid axis. Thyroid 18:1071 - 1085.	
2	Model Structure	General	The model assumes nearly all of T4 and T3 are bound to serum proteins with a small fraction free and it assumes perchlorate does not bind to plasma proteins. There is evidence that an increase in serum fT4 follows the administration of perchlorate and other anions (Machajlovskij and Langer, 1974) and fT4 levels return to normal when the anions are cleared, suggesting the displacement of the hormones by perchlorate or similar anions.	Binding assumptions should be explored and compared to any available data. Machajlovskij and Langer, 1974. Increase of serum free thyroxine following the administration of thiocyanate and other anions in vivo and in vitro. Acta Endocrinol 75:707-716.	S/M
3	Executive Summary	7, lines 22-23	The executive summary states the following about model predictions: "however, the lactating mothers were predicted to become hypothyroxinemic or hypothyroid at perchlorate exposures below 20 µg/kg/d"..." The criterion to predict hypothyroidism, TSH increase, is not included within the scope of the model, so hypothyroidism cannot be predicted.	Remove "or hypothyroid".	E
4	Introduction	9, lines11-12	Evidence for a relationship between maternal hypothyroxinemia during pregnancy and neurodevelopmental effects in infants/children	Consider developing a dose-response relationship between maternal fT4 during pregnancy and risk of neurodevelopmental	S/M

			appears to be better supported by the literature than effects of neonatal (postnatal) hypothyroxinemia on development are.	effects from available data irrespective of known perchlorate exposure. While a correlation between maternal and fetal fT4 is clearly expected, why not take advantage of the empirical data documenting a relationship between maternal fT4 and neurodevelopmental outcomes? The existing pregnant mother model could be used to compute effects of perchlorate exposure on maternal fT4 during pregnancy. Such an approach circumvents the arbitrary and ambiguous nature of selecting a particular percentile of fT4 as adverse effect.	
5	Introduction	12, lines 1-2	The introduction of Fisher et al. (2016) does not provide support for sensitivity of infants. The SAB report suggests such sensitivity is plausible, but does not provide any evidence for an effect, much less greater sensitivity.	Please use wording that more accurately reflects the content of the cited references, or eliminate the statement.	S
6	Introduction	17	A statistical definition for hypothyroxinemia is provided without addressing adversity associated with the definition for each lifestage considered in the model (mother, fetus, infant). Low levels of fT4, without consideration of other thyroid indicators, are not clearly adverse, as acknowledged by EPA.	Please indicate whether their hypothyroxinemia definition is meant to indicate bounding conditions within which the model is expected to be "reliable" or whether hypothyroxinemia, as defined here, is an adverse outcome at each lifestage.	S/M
7	BBDR Model	23	The document indicates that the PubMed search	Please clarify how references were identified	S/M

	Development and Parameterization		conducted to identify relevant papers for this activity occurred in December, 2013, almost three years ago. It does indicate that other papers were "later identified as potentially relevant", but does not indicate the mechanism by which additional papers where identified or set a clear literature cut off date. One of the primary data sets used for calibration has a publication date beyond the 12/2013 date (Gordon et al., 2014, as noted on p. 24).	after December 2013. Was it done systematically? EPA should conduct their own, updated PubMed search and review and provide the results to the reviewers/stakeholders, rather than shifting the burden of additional data identification to the reviewers (e.g., per Draft Charge Questions 1B and 3).	
8	BBDR Model Development and Parameterization	23	The text states that "62 articles had data that were used for calibration, validation or setting model parameters. Information for these 62 specific articles are provided in ReviewHERO416.xlsx. The review process was halted after it was judged that the objective had been met; i.e., sufficient data for model calibration had been identified." The statement that the review process was "halted" when "sufficient data had been identified" is unclear and confusing. Were all 62 articles reviewed and used? How was a threshold for "sufficient" data identified? Would more data not have the potential to improve model confidence? What possible actions in the review process were not pursued because "sufficient data" had been	Please provide this spreadsheet and clarify its data review process.	S/M

			identified? These statements seem contrary to the spirit of systematic review.		
9	BBDR Model Development and Parameterization	27-29	The model calibration process is not discussed in any detail, other than to state within the tables that certain parameters were fit visually to specified data sets.	Please indicate whether visual fitting was conducted in a certain sequence, or whether it was refined iteratively. When multiple data sets were used for calibration of a given parameter, EPA should indicate how different studies were weighted. The document should also indicate why visual fitting was used rather than a formal optimization process and discuss the implications for model confidence and precision.	S
10	BBDR Model Development and Parameterization	27-29	A primary goal of the public review of the BBDR documentation and model is understood to be an assessment of the scientific rigor of the model development and calibration/validation process. As such, complete transparency regarding calibration of model parameters is expected. Tables 4 and 5 should clearly indicate which plots show the data to which the parameters were fit. Reference (by figure number) to plots in previously published papers would be acceptable when models have not been appreciably altered. All plots for optimizations for the current effort should be shown. For example, T3 data were reportedly used to optimize the parameter T3FRAC_N), but	Please add figures where necessary (or add them to an Appendix) to document the model calibration process and then reference those figures (and existing figures in prior publications) in Tables 4 and 5.	S/M

			no fits are shown.		
11	Model Calibration Results and Summary of Calibration Results	60-68	The calibration results are characterized as: "Overall, the model predictions were considered adequate" (page 60). No scale, frame of reference, or justification for its characterization of the predictions as "adequate" is provided. Later (pp 62-8), the phraseology "within the range" of reported values is used repeatedly. At a minimum, the model should be judged on comparison to the central tendency of reliable data. While it is stated that "model predictions should roughly match average values in each data set", they frequently do not (e.g., Figure 5, Figure 7 upper panel). The criterion is justified as being "within the range" (a relatively low bar for model agreement) on the basis that only variability in iodide and perchlorate intake were considered. Despite consideration of a range of plausible intake values, a considerable fraction of the data frequently do fall outside of these ranges, sometimes by orders of magnitude (e.g., Figure 4, upper panel; Figure 5). Considering that no sensitivity analyses were presented specifically for urinary iodide concentrations (for example), the explanation that variability in physiological and biochemical factors "would	The criteria, and characterization of the agreement between data and simulations on some sort of a sliding scale, such as outstanding, excellent, good, fair, or poor needs to be provided. Metrics should be provided on the quality of agreement with particular model predictions (e.g., fT4 predictions vs. data on average within x-fold, or y % of data within x-fold). Rather than speculate regarding the source(s) of scatter in the experimental data, a sensitivity and variability analyses or Monte Carlo simulations of those outputs for which agreement was poor with the current model (which relies on central tendency parameter estimates only) should be conducted.	S/M

			also have significant effects on the metrics evaluated" is speculative and unsupported.		
12	Model Calibration Results	62	In Cao et al. (2010), urinary iodide and perchlorate data compared by infant feeding method are reported in units of µg/g creatinine, with geometric means and 95% confidence intervals, with no breakdown by postnatal day. Yet, in Figure 4, individual data are plotted as urinary iodide and perchlorate (µg/L) vs. postnatal day.	Please include how a greater level of detail than what was provided in the publication for any data set used in model calibration/validation was obtained.	S
13	Model calibration results	64-5	No rationale was provided for the suggestion that iodide levels in milk are not stable. An inability to characterize iodide concentrations in breast milk and thus the neonatal intake of iodide by breastfeeding babies calls into question the calibration of the lactating mother and infant thyroid hormone models.	A rationale for the lack of stability of iodide in milk should be provided. A rationale for how the breast-fed infant T4 model could be reliable when intake of iodide is so poorly characterized for this lifestage (Figure 7), and excretion of iodide frequently exceeds the predicted range (Figure 5) should also be provided.	S/M
14	Model Calibration Results	67	Individual NHANES data must be used with care because individual values are not a random sample; weights should be used.	Clarification should be provided regarding how NHANES sample weights were considered, if at all, in model calibration relying on that data.	S
15	Dose-Response Evaluation	69	Perchlorate (0-20 µg/kg/d) induced radio iodide uptake inhibition was simulated for the mother and were compared to adult data from Greer et al. (2002) data. However, Greer et al. also collected fT4, T4 and T3 data, which were not	Recommend simulating the thyroid hormone data as well and showing the simulations.	S

			compared.		
16	Dose-Response Evaluation	70-79	The derivation of bounds of the grey bands (depicting ranges for hypothyroxinemia) is not provided. Inconsistencies between the critical fT4 value for formula-fed infants vs. breast-fed infant, and for lactating women on different postnatal days are not explained. For example, for a 30-day-old formula-fed infant, 17.1 pM fT4 is the threshold for hypothyroxinemia, but the threshold for a 30-day-old breast fed infant is 18.1 pM.	The derivation of the bands should be described, also describe why breast-fed and formula-fed infants of the same age and lactating women at various times have differing criteria for being categorized as hypothyroxinemic and implications for establishing adversity. EPA should explain why fT4 levels below 12.1 pM would be adverse for a PND 7 lactating mother, while 8.94 pM is acceptable on day 30. The transient nature of varying definitions of hypothyroxinemia should be discussed in the context of establishing a Safe Drinking Water standard for perchlorate.	S/M
17	Local Sensitivity Analysis of BBDR Model With Perchlorate	83-91	Very little interpretation is provided for these analyses.	The discussion of the sensitivity analyses should be expanded.	S
18	Local Sensitivity Analysis of BBDR Model With Perchlorate	83-91	The sensitivity analysis neglected to report sensitivity to ingestion rates for iodide and perchlorate	Please determine and report the sensitivity of fT4 to maternal and infant iodide and perchlorate ingestion rates.	S
19	Appendix B	App 6	It is not clear why the third compartment of the thyroid was removed, when the earlier PBPK models of Merrill et al. (2003, 2005) and Clewell	This is key model structure should be expanded upon, rather than simplified. We also recommend providing simulations demonstrating	S/M

			et al. (2003a & 2003b, 2007) found it to be necessary to describe thyroid perchlorate and iodide time-course data. It is stated, "Dr. Fisher deemed this to be an unnecessary complication of the model." This statement does not provide adequate reasoning for removing a key physiological feature. Iodide compartmental models have also described the necessity for a three-compartmental thyroid (Lee et al., 1982), which captures the early phase of iodide uptake, consisting of trapping and organification processes and a slower phase of hormone accumulation and secretion.	the lack of difference between the two structures. Lee, P. W., Siegel, J. A., Harpen, M. D., Greenfield, M. A., and Verma, R. C. (1982). In vivo evaluation of intrathyroidal iodide metabolism. J. Clin. Endocrinol. Soc. 55, 1131â€"1137.	
20	Appendix D	App 20-23	The EPA switched to the "normal adult" urinary clearance parameter for the lactating mother and only had a minor difference during the first postnatal day from the "EPA 2009" model. There are not sufficient data to validate the lactating or postnatal mother's urine at this date. It appears more isn't done anything more with that parameter because it can't be validated.	However, another approach that could have been tried is scaling the perchlorate clearance rate during the first two weeks postnatal to that of the iodide urinary clearance shown in EPA 2009 Figure B-5 (data from Aboul-Khair et al. (1964)). Iodide clearance appears to be a little higher at birth (although part of the data is missing) and returns to normal around 6-12 days later.	S

Public Comments

Submitted By

Izze Kraiman

November 21, 2016

Joel Beauvais,
Deputy Assistant Administrator, Office of Water.

Dear Mr. Beauvais:

I am writing to you in response for your call to public comment regarding the safe drinking water act decision making on perchlorate and the Biological Base Dose-Response model that has been created. I am writing specifically concerning the proposed Maximum Contaminant Level of .7 μg/day. Taking into special consideration women and how their hormone levels will affect their baby.

After researching multiple studies and journal article .7 μg/day appears to be a safe MCL for men, women, and fetus'. These studies sampled urine and analyzed perchlorate levels as well as the amount of iodine present. Because the MCL is so important in combatting hypothyroxinemia proper research is necessary.

Overall, I think the EPA did a thorough job of analyzing how perchlorate affects humans and their iodine uptake into the thyroid gland. This number, .7 μg/day, will keep people safe from the health problems perchlorate can cause. Thank you for you time and consideration.

Sincerely,
Izze Kraiman
West Chester University

Introduction

The EPA has requested for public comment on their proposed MCL or Maximum Contaminant Level with special consideration towards pregnant women, developing fetuses, and breastfeeding mothers and children. Through research the EPA worked to produce a Biologically Based Dose-Response which analyzes how environmental factors such as perchlorate will affect a person on a molecular level. With help from the SAB (Science Advisory Board) the EPA worked to created an MCL to be used in consideration of the Safe Drinking Water Act. The number for MCL where no adverse health effects are seen in humans and no birth defects are seen in babies, is currently .7 μg/day. While some scientists believe this number could be raised slightly without seeing repercussions in human health, extensive research agrees with the number that the EPA has decided upon.

.7μg/day is the amount of perchlorate that a human can ingest and see no health problems. It is important to consider factors such as how a person can come in contact with perchlorate, what can happen if a person has excessive exposure, and how that can also affect a developing fetus. After assessing multiple sources of research .7 μg/day is a point that shows safe levels of the fT4 hormone and iodine in the urine.

Where does perchlorate come from

ClO_4 or Perchlorate is a naturally occurring in the environment as well as made for use in items such as fireworks, herbicides, and airbags in vehicles (Cook, 2015). Because this compound is found naturally occurring, especially in arid areas, and in many items a person comes in contact with, there must be an established safe limit for ingestion. Fruits, vegetables,

shellfish, and milk products all contain perchlorates. When they are cooked in areas with high levels in their water, these foods become even more unsafe (Asami et. al 2013).

Because proper hormones are necessary for a babies development, mother have to be aware of the common ways of ingestion for their children and fetuses. After birth, breast milk and formula are the main source of perchlorates for infants. On average, baby formula prepared with tap water was 1.11 μg/day. This number is high compared to the .7 μg/day suggested as the daily limit, but breast milk can have numbers up to five times higher (Asami et. al 2013).

Health risks perchlorate poses

When too much perchlorate is ingested, this ClO_4 will be a competitor for the uptake of iodide in the thyroid gland. Because of the nature of the thyroid, this will cause a decrease in the production of necessary hormones. These hormones are essential during pregnancy. which is one of the main concerns of hypothyroxinemia, the point at which adverse health effects are seen due to low level of the fT4 hormone. This is any level of fT4 below the 2.5^{th} percentile (Negro et.al 2013). Free thyroxine also known as fT4 is essential to the bodies proper metabolism and cellular function.

These hormones that the thyroid creates are essential to proper brain and neurological development in fetus'. In the first trimester it is essential for the mother to have enough fT4 due to the fact that the fetus relies exclusively on the mothers free thyroxine for its own thyroid regulation (Steinmaus et. al 2014). Because of the heavy reliance on proper thyroid function in mothers, it is important to come up with a Maximum Contaminant Level (MCL) so levels can be monitored.

Studies have been done to prove that increased levels of perchlorate will inhibit the fT4 hormone. One study looks at 2,299 participants all over the age of 12. This study has participants of multiple races, as well as 14% below the poverty line (Blount et. al 2006). Through blood and urine sampling, these scientists were able to show a correlation not only between perchlorate and fT4, but also iodine levels completing the link between the three. While it is agreed upon that these three levels all rely on each other, an acceptable level on ingestion needs to be established for the safety of everyone, especially developing fetus'.

Risks to Developing Fetus

Proper iodine intake during pregnancy is regularly talked about. This is important for many reasons, one being that a fetus has much less stored in its thyroid gland which can lead to iodine deprivation. A study shows that the highest 10% of hypothyroxinemic pregnant mothers saw a decreased average IQ score for their children at the age of 3, generally they were in the lower 10% of their age groups IQ score (Brent 2013). In these women, perchlorate was found in their urine and low iodine levels were noted.

Another study showed that women in the 10th percentile of hypothyroxinemia whose children were between 1 and 2 years old had lower scores on a cognitive development test known as Bayley Psychomotor Developmental Index (Negro et. al 2013). These reduced scores on exams that measure brain function are correlated to an increase in the incidence of diseases such as hyperactivity and attention deficit disorders. They are also linked to a delay in toddlers between the age of 18 and 30 months' ability to use expressive language as that age group should begin to do (Negro et. al 2013).

Analysis of perchlorate level studies

The Nutrition Examination Survey conducted a study assessing the amount of fT4 in men, women, and pregnant women. The women were broken further into iodine levels less then, and greater than 100 μg/L. The non-pregnant women who had iodine levels less than 100 μg/L, still have an fT4 number higher than those pregnant women. The data trend was the same with women who had iodine levels greater than 100 μg/L, pregnant women consistently had less fT4 then the equivalent non-pregnant females, as well as men (Suh et. al 2014). This data shows that pregnant women lack in fT4 hormone as the fetus requires it. With an excess ingestion of perchlorate these numbers would be even lower, which will have negative affects against the fetus.

There are a few ways to analyze iodine in the body to help find a correlation between iodine and perchlorate. One test is to look at the amount of iodine in someone's urine. This number will be around 90% of the amount consumed each day. Through the analysis of a sample of pregnant women, a curve was created to predict the correlation between amount of iodine and fT4 levels. As seen unanimously as iodine levels go up, fT4 levels go up as well. This study saw that at an ingestion level of perchlorate 1.0 μg/day, the fT4 levels began to match up with those associated with hypothyroxinemia (Lumen 2013). Based on this data, a number less than 1.0 μg/day would be an acceptable MCL. This aligns with the proposed .7 μg/day that the EPA suggested as a point without adverse health effects.

A 2007 study that the EPA used to determine an MCL for perchlorate studied a group of 21 women and 16 men between the ages of 18 and 57 a variety of doses of perchlorate for 14 days. The dose amounts were 0.007, 0.02, 0.1 and 0.5 mg perchlorate/kg body weight (Greer et. al). The individuals in the study that saw no adverse health effects on thyroid iodine uptake

where those those who received .7μg/day. Any number after saw an 83.6% decrease in their thyroid function, a number that could potentially effect health.

While this study has been key in determining the MCL, the sample of people was small, and it did not take into consideration any intersectional approach for example race. It was over a short period of time which may not show the long term health effects that perchlorate can have on the body.

One study that takes an interesting aspect on perchlorate intake had three different groups. One was given a placebo dose, one was given .5 μg/day and one was given 3 μg/day. While these were extremely small sample sizes with only 5 participants in each, the evidence was very telling. The placebo group as expected staying within a fraction of their baseline values for fT4. The group that received .5 μg/day almost no change while the group that was given 3 μg/day, saw a slight decrease in fT4 (Braverman et. al 2011). This study and the information it provides is important. While the sample size may be small, these levels were assessed long term for 6 months of daily ingestion.

This information helps when assessing an MCL and how over time it may affect hormone levels. Because these numbers correlate with previous studies showing that 3μg/day shows problems in human health. While the .5 μg/day is slightly lower than the .7 μg/day that the EPA suggests, the general curve of the data agrees.

Conclusion

There is a strong correlation between the amount of perchlorate ingested, iodine intake, and essential hormones in the human body. Lack of these hormones and iodine can lead to serious health problems especially in pregnancy women and their fetus' including cognitive

problems and lower IQ scores. The EPA has decided that .7 μg/day is a safe ingestion level of perchlorates and that hypothyroxinemia will not be seen, keeping mothers and children safe. Through research and analyzing multiple well respected studies, there has been no health problems associated with this number. Until solid research comes out with a strong sample size and number showing otherwise, .7 μg/day will be the universally accepted safe amount of perchlorate ingestion without any adverse health effects.

References

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Public Comments

Submitted By

The Chlorine Institute

THE CHLORINE INSTITUTE
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U. S. Environmental Protection Agency
Office of Ground Water and Drinking Water
Standards and Risk Management Division
1200 Pennsylvania Avenue NW.
Washington, DC 20460

November 23, 2016

RE: Request for Public Comments to be sent to EPA on Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate, Docket ID Number: EPA-HQ-OW-2016-0438

Dear Sir or Madam:

The Chlorine Institute ("CI" or the "Institute") is a 190 member, not-for-profit trade association of chlor-alkali producers worldwide, as well as packagers, distributors, users, and suppliers. The Institute's North American Producer members account for more than 93 percent of the total chlorine production capacity of the U.S., Canada, and Mexico. The Institute's mission chemicals, namely chlorine, sodium hydroxide and potassium hydroxide, and hydrogen chloride, are used throughout the U.S. economy and are paramount to the protection of public health.

While The Chlorine Institute appreciates EPA's efforts in developing a standardized model for the purpose of determining an appropriate perchlorate drinking water level, the Institute believes there are flaws in the BBDR model that should be considered. CI provides the following comments to further explain the flaws in the model.

Lack of data or limited data is noted for the life-stage human values.

- The proposed BBDR model used physiological parameters to set the life-stage-specific human values. However, throughout the document on several occasions, the lack of data or limited data is noted for the life-stage human values. As noted by EPA, "Physiological parameters are life-stage specific, and were taken from appropriate sources (identified in the data tables) where possible. However, many of the iodide/thyroid hormone and perchlorate parameters where not available for specific life-stages, and so were extrapolated from other life-stages or in-vitro data." (US EPA, 2016)[1]. One parameter with limited or no data is hypothyroxinemia during pregnancy, maternal lactation or infancy as noted by EPA. In addition, there is no clinical definition of hypothyroxinemia and, as a result, various ranges of free T4 (fT4) are found in the literature. As noted by EPA, " within the context of pregnancy, some authors use the

2.5th percentile of the fT4 population distribution while others use the 10th percentile and the reference ranges vary between populations and studies (Moleti et al., 2011)[2]. Elevated TSH levels, the marker of hypothyroidism, can occur in women with fT4 levels in the same range as other women with normal TSH levels (e.g., see 9 Figure 1 in Moleti et al. (2008), so there is also not a specific fT4 level below which this transition occurs" (US EPA, 2016). Therefore, assumptions have been made to set the parameters for the model that may weaken the predictive outcomes of the model.

The BBDR model does not account for both aggregate and cumulative exposures to chemicals with the same mode of action to perchlorate.

- The proposed BBDR model does not account for chemicals with similar modes of action that inhibit the sodium iodide symporter (NIS) which transports iodine into the thyroid. Perchlorate is known to inhibit the NIS. However, so are nitrate and thiocyanate which are ubiquitous in a healthy diet and drinking water. Background levels of these chemicals can be much higher than perchlorate and are unlikely to be distinguishable. In regards to their potency, in vitro studies comparing the relative abilities of perchlorate, nitrate, and thiocyanate to inhibit cellular iodine uptake show that, after adjusting for biological half-life, perchlorate is half as potent as thiocyanate and 240 times as potent as nitrate (De Groef et al. 2006)[3]. In addition, ATSDR (2008)[4] noted that, "Nitrate and thiocyanate are widely distributed in nature and, because both anions also inhibit RAIU [radioactive iodide uptake], as demonstrated by Tonacchera et al. (2004)[5], should also be included in the discussion of the effects of inhibition of the NIS by anions." The BBDR model does not account for both aggregate and cumulative exposures to chemicals with the same mode of action to perchlorate.

Appropriate data are not available to validate the model.

- The infant, 7 to 90 days of age, breast-fed and formula fed, as well as the lactating mother were selected for the BBDR model development to address the most sensitive period of thyroid function maturation that may have consequences if exposure to perchlorate occurs. There is, however, a lack of epidemiologic data that current environmental exposure to perchlorate results in adverse effects to infant thyroid function (Tarone et al. 2010[6]; Charnley 2008[7]). Without the appropriate data, the model cannot be validated. If the appropriate data are not available to validate the model, then data must be collected from biomonitoring studies or generated in animal prior to use of the model to most accurately predict outcomes from exposures to perchlorate.

Homeostatic control mechanism does not account for in the proposed BBDR model.

- Clearly, a reduction in thyroid hormones over a substantial amount of time during fetal development is potentially deleterious to the developing fetus. However, the thyroid

has stores of iodide received from the mother such that short-term fluctuations in iodide uptake in the first post-natal days will cause no effect. Physiologically, when uptake of iodine is decreased, the body adapts by upregulating the number of the NISs to pump more iodide into the thyroid. This is a homeostatic control mechanism and is not accounted for in the proposed BBDR model.

Additional resources to be reviewed and considered in proposed BBDR model.

- Lumen et al. (November 2016)[8] have published a population based pregnancy model that estimates iodine nutrition and thyroid status in late gestation pregnant women in the United States. The BBDR model accounts for a wider range of iodine deficiencies and homeostatic mechanisms. To characterize total (T4) and free (fT4) thyroxine levels for a given iodine status at the population-level, the distribution of iodine intake for late-gestation pregnant women in the U.S was reconstructed using various reverse dosimetry methods and available biomonitoring data. The reconstructed distributions of iodine intake allowed for the estimation of nutrient inadequacy for late-gestation pregnant women in the U.S. via the probability approach. The prevalence of iodine inadequacy for third-trimester pregnant women in the U.S. was estimated to be between 21% and 44%. This paper should be reviewed and considered for incorporation into the proposed BBDR model (Lumen, 2016).

- In May 2011, The Chlorine Institute commissioned an evaluation (attached) conducted by ENVIRON International Corporation on the health advisories and standards for perchlorate levels in drinking water. This evaluation was submitted to EPA in response to its Final Regulatory Determination, which was issued in February 2011 for the agency to proceed with derivation and proposal of a National Primary Drinking Water Regulation. In that evaluation, ENVIRON provides what the Institute believes to be an acceptable perchlorate drinking water level based on appropriate data. The ENVIRON evaluation is another resource that should be reviewed and considered by EPA to further develop the BBDR model.

Peer review process

- The Federal Register notice of September 30, 2016 states that "Versar, Inc., will provide a report to EPA summarizing the peer reviewer's [sic] evaluation of the scientific and technical merit of the draft model and draft report and their responses to the charge questions." Due to the complexity of the model and the SAB Perchlorate Panel's call for transparency, like the SAB process, the panel should be responsible for drafting the report, not the contractor Versar. Additionally, it is unclear whether Versar has the necessary expertise to summarize the complex science and science policy questions

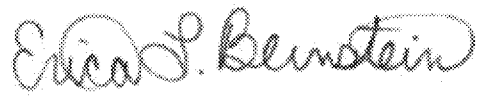
involved with the BBDR model and therefore may not accurately reflect the issues, conclusions, and recommendations of the panel.

Conclusion

In conclusion, the Institute believes the BBDR model does not account for both aggregate and cumulative exposures to chemicals with the same mode of action to perchlorates and that there is a lack of data to validate the model. CI recommends that EPA consider the comments and resources noted above, as well as review the attached ENVIRON study, to further improve the BBDR model in the agency's effort to propose an appropriate perchlorate drinking water level.

Thank you for the opportunity to comment on this proposed model and your careful attention.

Best Regards,



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Evaluation of Health Advisories and Standards for Perchlorate Levels in Drinking Water

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ACRONYMS

ADHD	Attention Deficit Hyperactivity Disorder
BMD	Benchmark Dose
BMDL	Lower statistical limit on a benchmark dose
Cal EPA	California Environmental Protection Agency
CATS	Controlled Antenatal Thyroid Screening Study
DWS	Drinking Water Standard
HA	Health Advisory
kg	Kilogram
Mass DEP	Massachusetts Department of Environmental Protection
MCL	Maximum Contaminant Limit
mg/kg/day	Milligrams per kilogram per day
µg/g	Micrograms per gram
µg/L	Micrograms per liter
NHANES	National Health & Nutritional Examination Survey
NIS	Sodium-Iodide Symporter
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NPDWR	National Primary Drinking Water Regulation
NRC	National Research Council
PCH	Primary Congenital Hypothyroidism
PHG	Public Health Goal
RAIU	Radioactive Iodine Uptake
RfD	Reference Dose
RSC	Relative Source Contribution
TBG	Thyroxine Binding Globulin
T_3	Triiodothyronine
T_4	Thyroxine
Tg	Thyroglobulin
TSH	Thyroid Stimulating Hormone
TRH	Thyrotropin Releasing Hormone
UCMR 1	First Unregulated Contaminant Monitoring Regulation
UF	Uncertainty Factor
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration

Executive Summary

Perchlorate's effect on the thyroid to inhibit iodide uptake has been known for decades and has been the reason for the use of high doses of perchlorate, therapeutically, to treat hyperthyroidism, in particular in the treatment of Graves disease, a medical condition resulting from hyperthyroidism. Other non-medical uses of perchlorate, such as in rocket fuel and other applications as an oxygen source in high burn applications, may have resulted in releases of perchlorate to the environment, particularly to ground water.

Studies in laboratory rats have raised a concern that exposure to perchlorate may result in adverse effects in people with normally functioning thyroids. While the function of the thyroid and the homeostatic mechanisms for maintaining thyroid function at biologically relevant levels are similar across species, rats are more sensitive to perchlorate-induced hormone changes than humans. Fundamental differences between rats and humans are the reduced ability in rats to store thyroid hormones in the thyroid gland and the inability to have a substantial "backup" supply maintained by special proteins in the blood. Thus, the dose-responses for adverse effects reported in rats may not be directly applicable to use in human risk assessment of exposure to perchlorate.

Human epidemiological, occupational, and clinical studies, taken together, indicate that perchlorate exposures at environmental and occupational levels do not produce changes in thyroid function that would be considered adverse and affect normal thyroid functioning. While very short-term exposure to perchlorate may produce a transient change in thyroid hormone levels, the resilient, adaptive mechanisms that maintain homeostasis (a dynamic and controlled balance) in humans restore the balance of thyroid hormone levels in the thyroid and circulating blood. In people, even with long term exposure to perchlorate, the thyroid system is able to control these fluctuations and conserve thyroid hormone levels in the blood to maintain normal function. Thus, inhibition of thyroid iodide uptake is not an adverse effect unless extreme conditions occur, such as chronic inhibition from extremely high (i.e., therapeutic levels) exposures. In the case where adequate iodine is in the diet, exposure to perchlorate at environmentally relevant levels should not be of concern.

Despite these experimental and physiological data, the U.S. Environmental Protection Agency (USEPA), California Environmental Protection Agency (Cal EPA), and Massachusetts Department of Environmental Protection (Mass DEP) have derived perchlorate drinking water advisories or standards based on human clinical data for inhibition of iodide uptake into the thyroid from a 2-week drinking water exposure. This biological endpoint was recommended by a National Research Council (NRC) committee in 2005, which noted that the effect was not adverse, but was conservatively useful for developing a safe drinking water level. However, data published at the same time or after the NRC recommendation clearly indicated that environmental perchlorate exposure levels can be handled without injury by adaptive biological mechanisms and confirmed the NRCs conclusion that such levels do not have an adverse impact on thyroid function, even in iodide-deficient pregnant women and infants.

This present report evaluated the data considered by the NRC committee and regulatory agencies and more recent data published since their evaluations. We are proposing an

acceptable drinking water level of 620 µg perchlorate/L, based on a dose-response analysis of the No Observed Adverse Effect Level (NOAEL) from human occupational studies. While our proposed value is higher than those proposed by USEPA, Cal EPA, and Mass DEP, our recommended drinking water level is scientifically defensible and was derived with conservative choices for defining the effect threshold that would be protective of sensitive subpopulations.

1 Introduction

The ability of perchlorate to affect human thyroid function has been known for decades. In the 1950s and 60s, high oral doses of perchlorate (2000 mg/day in adults) were used medicinally to treat hyperthyroidism ("overactive thyroid"). Although high-dose treatments were discontinued in the late 1960s, lower doses (600 mg/day) continued to be used without serious side effects to treat anti-thyroid effects of the drug, amiodarone (Leung et al., 2010). Perchlorate does not affect organ systems in humans other than the thyroid.

The use of perchlorate in non-medical applications, such as an oxygen source in high burn rate combustion applications, such as solid rocket fuels, explosives, road flares, pyrotechnics, and air bag inflation systems, may have resulted in the release of perchlorate in the environment, where it has been detected in ground water of 26 states (Trumbo, 2009; Braverman, 2007).

Regulatory agencies in the United States, based largely on animal data and data in a very short-term study in human volunteers, have assumed that the presence of perchlorate in drinking water could have an impact on normal thyroid function with resultant adverse impacts on health. While the potential amount of perchlorate intake from drinking water is likely to be orders of magnitude lower than those historically used in medical therapy, California Environmental Protection Agency's (Cal EPA) Office of Environmental Health Hazard Assessment (OEHHA) derived a Public Health Goal (PHG) for perchlorate in drinking water in 2004, which became the Maximum Contaminant Level (MCL) in 2005. Likewise, Massachusetts Department of Environmental Protection (Mass DEP) derived a perchlorate drinking water standard in 2006. In 2008, the U.S. Environmental Protection Agency (USEPA) issued a Preliminary Regulatory Determination (USEPA, 2008a), indicating that a national primary drinking water regulation for perchlorate would "not present a meaningful opportunity for health risk reduction for persons served by public water systems." USEPA did calculate a Health Advisory (HA) Level for drinking water (USEPA, 2008b). IN February of 2011, USEPA issued a Final Regulatory Determination to proceed with derivation and proposal of a National Primary Drinking Water Regulation (NPDWR) (USEPA, 2011a) within 24 months.

Although the USEPA, Cal EPA and Mass DEP values differ, they are all based on the same clinical study in which volunteers ingested perchlorate in drinking water for two weeks, (Greer et al., 2002). The differences between the values derived by these groups result from different methodological approaches used to determine the allowable total daily dose of perchlorate, the proportion of that dose allowed in drinking water, the drinking water ingestion rate, and treatment of data uncertainties (Sections 2.1-2.3). The regulatory values are based on opinions of the National Research Council (NRC) presented in a 2005 assessment of the perchlorate data in humans and animals (NRC, 2005).

Newer and more relevant data are now available. For this report, ENVIRON examined and performed a critical review of the latest data. A summary of the biology and function of the thyroid hormone system relevant to perchlorate, relevant animal and human data used by the USEPA, Cal EPA, and Mass DEP to set acceptable values for perchlorate in drinking water, and data published since the NRC (2005) assessment are presented in the Appendix. A critical evaluation of the existing USEPA, Cal EPA, and Mass DEP perchlorate drinking water

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standards is presented in Section 2. Based on this review, ENVIRON has proposed a scientifically defensible acceptable drinking water level for perchlorate, presented in Section 3.

2 Evaluation of the Drinking Water Levels for Perchlorate by Regulatory Agencies

As detailed in the Appendix, the effect of perchlorate on the thyroid is to inhibit the uptake if iodide from the blood into the thyroid follicle cells, where iodine is used to produce the hormone thyroxine (T_4), which is then converted enzymatically to triiodothyronine (T_3). The USEPA, Cal EPA, and Mass perchlorate drinking water values are all based on the data from Greer et al. (2002), in which 37 adults were given 0.007, 0.02, 0.1, or 0.5 mg/kg/day perchlorate (groups of 7-10 subjects) in drinking water for 14 days. After 2 and 14 days of exposure, the uptake of radioactive iodide (RAIU, a representative fraction of iodide in the whole body) into the thyroid was measured. In addition, blood levels of perchlorate and thyroid hormones T_3, T_4, and thyroid stimulating hormone (TSH) were measured before, during, and after cessation of exposure. While significant inhibition of RAIU was observed at ≥0.02 mg/kg/day, there were not associated with changes in thyroid hormone levels. A lack of change in thyroid hormones is not surprising, as healthy adult thyroids contain sufficient stores of T_3 and T_4 to maintain normal hormone levels in the body for up to six months.

Studies published since the NRC (2005) assessment indicate that the human thyroid system compensates for inhibited iodide uptake from chronic environmental and occupational perchlorate exposure, maintaining adequate thyroid function in clinical volunteers (Braverman et al., 2006), perchlorate workers (Lamm et al., 1999; Braverman et al., 2005), and in iodine-deficient women and pregnant women and their infants (Crump et al., 2000; Tellez et al., 2005; Buffler et al., 2006; Van Landingham and Gibbs, 2008; Pearce et al., 2008, 2010, 2011). Compensation for inhibition of iodide uptake is accomplished by stimulation of the thyroid to increase the capacity of iodide transport into the thyroid follicle cells. This is one of the functions of adaptive, resilient biological feedback mechanisms that are inherent in all humans to maintain homeostasis and normal thyroid health, as discussed in the Appendix. Thus, a 2-week exposure (Greer et al., 2002) is not characteristic or predictive of long term functioning at such low levels of perchlorate exposure. Nevertheless, the NRC derived a Reference Dose (RfD) of 0.0007 mg/kg/day (0.7 µg/kg/day) based on a perchlorate No Observed Effect Level (NOEL) producing no significant short-term inhibition (less than 2%) of RAIU. The NOEL of 0.7 µg/kg/day was divided by an uncertainty factor (UF) of 10 to account for sensitive subpopulations. In the same assessment, NRC stated that

> ***"it is not likely that the decreases in thyroid iodide uptake reported in short-term studies would be sustained; rather, iodide uptake would be expected to return to normal. To cause declines in thyroid hormone production that would have adverse health effects, iodide uptake would most likely have to be reduced by at least 75% for months or longer."***

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Derivation of a scientifically-valid, acceptable perchlorate drinking water level should be based on a dose estimate that is close to, but below, the actual threshold for onset of the most sensitive adverse effect (subclinical hypothyroidism). For perchlorate, this calls for chronic exposure data in humans that identifies an exposure level in which the thyroid has achieved non-adverse compensation for iodide uptake inhibition, while maintaining adequate thyroid hormone production. Nevertheless, USEPA, Cal EPA, and Mass DEP adopted inhibition of thyroidal iodide uptake reported by Greer et al. (2002) as the critical endpoint for derivation of their respective drinking water values. Short-term inhibition of iodide uptake is an inappropriate endpoint for deriving a safe drinking water level for perchlorate because (1) it is not an adverse effect, (2) it does not result in changes in thyroid hormone levels or function, and (3) the thyroid system compensates for the inhibition to maintain adequate thyroid hormone levels. The USEPA, Cal EPA, and Mass DEP perchlorate drinking water levels, based on a short-term NOEL, are no more health protective than higher levels that are based on a long-term No Observed Adverse Effect Level (NOAEL). As discussed in Section 3 and the Appendix, the available human data for perchlorate indicate higher exposure levels than the Greer et al. (2002) NOEL that result in initial inhibition of iodide uptake, but produced no adverse effect on thyroid hormone levels or thyroid tissue health (i.e., a NOAEL).

2.1 U.S. EPA Interim Drinking Water Health Advisory for Perchlorate

The USEPA (2008) Interim Health Advisory (HA) for perchlorate in drinking water is 15 µg/L. The HA is based on the NRC (2005) and USEPA (2005) RfD of 0.7 µg/kg/day (i.e., Greer et al. [2002] NOEL divided by 10). The fraction of the total dose (such as an RfD) of a regulated chemical allowable in drinking water, accounting for other non-drinking water exposures, is called the Relative Source Contribution (RSC). For example, if a hypothetical daily estimated perchlorate exposure from sources other than drinking water were 25% of the RfD, the perchlorate exposure allowed from drinking water would be 75% of the RfD, resulting in an RSC of 0.75. In the U.S., the main source of non-drinking water perchlorate exposure is food, such as vegetables and dairy products, with daily intake estimates ranging from 0.08-0.4 µg/kg/day (Trumbo et al., 2010). Data for perchlorate intake in food are available from the National Health and Nutritional Examination Survey (NHANES), the First Unregulated Contaminant Monitoring Regulation (UCMR 1), and the U.S. Food and Drug Administration (USFDA) Total Diet Study. USEPA analyzed the NHANES and UCMR 1 databases to derive an estimate of 0.263 µg/kg/day for dietary perchlorate ingestion in pregnant women. This value is 38% of the USEPA RfD, allowing for 62% of the RfD to be allowed in drinking water (RSC = 0.62). Finally, USEPA used a body weight (BW) and daily drinking water ingestion rate (IR) of 70 kg and 2L/day, respectively, both of which are default values used in deriving drinking water health advisories. Using these values, the interim drinking water HA level was calculated as:

$$HA = \frac{\frac{NOEL}{UF} \times RSC \times BW}{IR}$$

$$HA = \frac{\frac{7\mu g/kg/day}{10} \times 0.62 \times 70kg}{2L/day} = 15\ \mu g/L$$

USEPA selected the inappropriate endpoint (inhibition RAIU) on which to base the RfD and the HA, for reasons discussed in Section 2.0. The selection of an RSC of 0.62 is based on NHANES and UCMR 1 data for pregnant women living in areas unlikely to have perchlorate in drinking water. With an estimate of perchlorate in food of 0.263 µg/kg/day, selection of an RfD of 0.7 µg/kg/day allows for only 62% of total perchlorate intake to come from drinking water. However, there is uncertainty as to whether an RSC is at all necessary, as the perchlorate levels in diet of volunteers were not monitored and may have resulted in total daily perchlorate intake higher than the known doses administered in this study. Thus, the Greer et al. (2002) NOEL on which the USEPA RfD was based may have been underestimated.

2.2 Evaluation of the California EPA Drinking Water MCL for Perchlorate

In 2004, Cal EPA promulgated a primary MCL for perchlorate in drinking water, based on the derivation of a Public Health Goal (PHG) of 6 µg/L, as described by OEHHA (OEHHA, 2004) and Ting et al. (2006). The MCL was based on Cal EPA's benchmark dose (BMD) modeling of the data from the study of Greer et al. (2002), in which a 5% decrease in RAIU was considered biologically significant. From the BMD modeling, a statistical lower limit (i.e., confidence bound) of the benchmark dose (BMDL), 3.7 µg/kg/day, was estimated. The BMDL incorporates information on the shape of the dose-response curve (i.e., potency), as well as variation in the experimental measurements. The BMDL served as a surrogate No-Observed-Effect-Level (NOEL) (USEPA, 2000), and was divided by an UF of 10 to account for uncertainties in sensitivity of iodide-deficient hypothyroid pregnant women and their fetuses and infants. Data for perchlorate in some foods were analyzed by Cal EPA (Kirk et al., 2003, as cited by USEPA, 2008) to qualitatively determine that more than half of environmental perchlorate exposure is likely to come from drinking water rather than food. Thus, an RSC of 0.60 was selected (OEHHA, 2004). Finally, Cal EPA used a body weight-to-daily drinking water ingestion rate ratio of 25.2 kg/day/L (61kg body weight; 2.42L/day) to represent drinking water consumption for the 95th percentile of pregnant women (OEHHA, 2000). Using these values, the Cal EPA primary MCL was calculated as:

$$MCL = \frac{\frac{3.7\mu g/kg/day}{10} \times 0.60 \times 61\ kg}{2.42L/day} = 6\ \mu g/L$$

Cal EPA selected the inappropriate endpoint (inhibition of RAIU) on which to base MCL. Further, Cal EPA's selection of an RSC of 0.60 is based on the assumption that perchlorate in drinking water accounts for most of the perchlorate exposure. Data for perchlorate in the diet of various U.S. subpopulations, including adults, children, and pregnant and lactating women, are now available from the NHANES and UCMR databases, as well as the U.S. Food and Drug Administration (USFDA) Total Diet Study. Selection of an RSC should be based on a reasonable quantitative estimate of relative food contribution to the total allowable perchlorate dose, rather than an arbitrarily-chosen fraction.

2.3 Evaluation of the Massachusetts DEP Drinking Water MCL for Perchlorate

In 2006, Massachusetts DEP promulgated a Drinking Water Standard (DWS, Massachusetts' nomenclature for an MCL) for perchlorate of 2 µg/L, as described by Zewdie et al. (2008). Mass DEP defined an RfD for perchlorate by dividing the Greer et al. (2002) NOEL of 7 µg/kg/day for inhibition of RAIU by a composite UF of 100. In addition to lowering the NOEL by a factor of 10 to account for uncertainties in sensitivity of iodide-deficient of hypothyroid pregnant women and their fetuses and infants (as done by USEPA and Cal EPA), another factor of 10 was applied for "database insufficiencies", extrapolation of results from healthy adults, and basing the drinking water standard on what Mass DEP defined as an adverse effect level rather than a NOEL. An RSC of 0.20 was applied to the Mass DEP RfD, allowing for 20% of the total daily perchlorate dose to come from drinking water. Finally, Mass DEP used default adult body weight and daily drinking water ingestion rate values of 70 kg and 2L/day, respectively. Using these values, the Mass DEP DWS was calculated as:

$$DWS = \frac{\frac{7\mu g/kg/day}{100} \times 0.20 \times 70kg}{2L/day} = 0.49\ \mu g/L$$

Although the calculated DWS is <0.5 µg/L, Mass DEP set the DWS at 2 µg/L. Mass DEP stated that standard use of sodium hypochlorite for public drinking water disinfection may result in finished drinking water with perchlorate levels in excess of 1 µg/L. In order to avoid creation of compliance issues creating a disincentive for necessary water supply disinfection, the DWS was set at 2 µg/L.

Mass DEP selected the inappropriate endpoint (short-term inhibition of RAIU) on which to base their RfD and DWS. In addition to applying an UF of 10 for uncertainties in sensitivity of subpopulations, Mass DEP applied an additional UF of 10 for data gaps. Mass DEP determined inhibition of RAIU in 4 of 7 volunteers in the low-dose group of the Greer et al. (2002) study to be an adverse effect rather than a NOEL, in spite of the fact that the group as a whole did not exhibit significant RAIU inhibition or any reduction in thyroid function. Categorizing short-term inhibition of RAIU as an adverse effect is in opposition to the findings of the NRC (2005) panel, as well as the occupational and epidemiological studies discussed above and in the Appendix that indicate the compensatory ability of the thyroid hormone system to maintain normal thyroid function in adults, pregnant women, and their infants. This decision resulted in an inappropriately conservative RfD on which to base the DWS.

The 2004 selection of an RSC of 20% is based on Mass DEP's determination at the time that the available data did not support the derivation of a less conservative value. In retrospect, Zewdie et al. (2008) discussed the NHANES, UCMR, and USFDA Total Diet Study data. These authors determined that, given the low Mass DEP RfD of 0.07 µg/kg/day relative to food perchlorate intake estimates of 0.2-0.4 µg/kg/day, an RSC of 20% or less was justified. However, Mass DEPs choice to use an inappropriate endpoint and an unnecessarily high UF also resulted in an unnecessarily conservative RSC.

2.4 Limitations of Existing Drinking Water Advisories and Standards

The perchlorate drinking water health advisory and standards derived by USEPA, Cal EPA, and Mass DEP are overly conservative and not based on appropriate interpretation of the available human clinical, epidemiological, and occupational data. All are flawed because they are based on a short-term, non-adverse effect (inhibition of RAIU) from a 2-week exposure in healthy adult volunteers that does not inform on the compensatory mechanisms of the thyroid hormone system to maintain homeostasis during chronic exposure, which are indicated in the human data from chronic exposures. In addition, Mass DEP incorrectly categorized short-term inhibition of RAIU as an adverse effect and applied an additional, unnecessary UF of 10. A consequence of selecting the Greer et al. (2002) NOEL of 7 µg/kg/day as the point-of-departure for deriving a drinking water standard, and applying UFs of 10 or 100, is that the resulting total allowable perchlorate dose (0.07-0.7 µg/kg/day) is at or less than the levels consumed in food (0.08-0.4 µg/kg/day). This forces down the fraction of total perchlorate allowed in drinking water by application of smaller and unnecessarily conservative RSCs. These issues resulted in allowable drinking water levels of 2-15 µg/L that may be problematic for compliance by some public water systems, while providing little, if any, real meaningful reduction in public health risk.

3 Acceptable Drinking Water Level for Perchlorate

ENVIRON derived an acceptable drinking water level for perchlorate based on dose-response data from chronic human exposures. The present assessment is based on data from chronic human exposures reported by Braverman et al. (2004) and Lamm et al., 1999. These data are preferable for several reasons. The study subjects, perchlorate production workers, were exposed for a minimum of 1.7 years and an average of 6 years.

Exposure of the perchlorate workers were primarily via inhalation. However, estimates of the total daily perchlorate dose were calculated using perchlorate levels measured in blood and urine by the study authors (Lamm et al., 1999; Braverman et al., 2004). Regardless of whether perchlorate is inhaled or ingested, equivalent levels in the blood will have the same effect on the thyroid system. Thus, inhalation exposures can be extrapolated to oral exposures using data for perchlorate blood and urine levels of perchlorate as well as knowledge of how quickly perchlorate is cleared from the body (as done by Crump and Gibbs [2005], discussed below).

The perchlorate workers and controls were observed before, during, and after three consecutive 12-hour work shift exposures for inhibition of RAIU (Braverman et al., 2004) and thyroid function (T_3, T_4, TSH, FTI [free T_4 index], and thyroglobulin levels) (Lamm et al., 1999; Braverman et al., 2004). Blood and urinary perchlorate levels for individual workers were available for analysis. Braverman et al. (2004) also measured levels of the inhibitors of iodide uptake that are ubiquitous in the diet, thiocyanate and nitrate, in order to isolate the effects of perchlorate exposure. Because thiocyanate and nitrate levels were not different between control and exposed workers, any differences seen RAIU or thyroid function could be attributed to perchlorate exposure.

Although RAIU inhibition was reported in the exposed workers, upregulation of iodide uptake capacity was also exhibited. Prior to the first observed work shift, the average thyroid RAIU for twenty-nine exposed workers was 21.5%, compared to 14.4% for twelve controls (Braverman et al., 2004). Even though the median exposures of 0.33 mg/kg/shift occurred in 3-day on/3-day off shifts, the workers experienced a compensated ability to get the required amount of iodide into the thyroid, even in the presence of perchlorate-induced inhibition. The study authors suggested that higher pre-shift values of RAIU in exposed workers are indicative of upregulation of iodide uptake. During the exposure, the inhibition of iodide uptake by perchlorate reduced the rate of RAIU from 21.5% down to 13.5%, which was essentially equal to the unexposed controls (14.4%). These findings, coupled with the lack of change in thyroid hormone levels or thyroid gland size, showed that chronic occupational perchlorate exposure was dealt with effectively by the hypothalamus-pituitary-thyroid axis, providing protection from subclinical hypothyroidism.

Crump and Gibbs (2005) analyzed the occupational data of Braverman et al. (2004), Lamm et al. (1999), and the data of Greer et al. (2002). They used simple, single-compartment mathematical models of the body to extrapolate the inhaled daily doses from the blood and urine perchlorate levels. The accuracy of the models to predict daily perchlorate doses were confirmed against the multi-day perchlorate blood level data from subjects in the Greer et al. (2002) study. They then performed BMD modeling of the worker dose data to estimate a perchlorate dose that would have no effect on thyroid function. Rather than modeling data for inhibition of iodide uptake (as was done by Cal EPA), Crump and Gibbs (2005) modeled changes in blood levels of thyroxine (T_4) or thyroid stimulating hormone (TSH), two thyroid hormones that are the primary indicators of thyroid function. Because no clinically abnormal T_4 or TSH levels were measured in the workers, Crump and Gibbs (2005) selected blood levels that were different from 95% of the study population as their surrogate threshold of response for the purposes of modeling the data. The resulting BMDLs were 24 mg/day (based on free T_4 in the blood) and 57 mg/day (based on TSH in the blood). Assuming an average worker body weight of 96 kg (201.3 lbs for exposed workers in Braverman et al., [2004]), the more conservative of the two no-response levels, 24 mg/day, would result in a body weight-adjusted BMDL of 0.25 mg/kg/day, or 250 µg/kg/day, that could be used as a point of departure for deriving an RfD and acceptable drinking water level. An RfD of 25 µg/kg/day was calculated by dividing the BMDL of 250 µg/kg/day by an uncertainty factor of 10 to be conservatively protective of potentially sensitive subpopulations, if any. The ENVIRON RfD is higher than the RfD USEPA (2005, 2008) an Cal EPA (2004) because of the selection of subclinical hypothyroidism from chronic perchlorate exposure as the critical endpoint, which is a more appropriate endpoint than inhibition iodide uptake from short-term exposure.

The derive an appropriate drinking water level for perchlorate, representative body weights and ingestion rates from the most sensitive population should be used, if data are available. Although the human data do not indicate that infants exposed *in utero* of iodide-deficient women are affected by environmental perchlorate exposures (see Appendix), this subpopulation was selected to base an acceptable drinking water level. Thus, ENVIRON calculated an acceptable perchlorate drinking water level using estimates of perchlorate in food, body weight, and water ingestion rate data for pregnant women.

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Using data from the NHANES and UCMR data sets, USEPA estimated perchlorate intake from food in 90% of pregnant women in the U.S. would likely be 0.263 µg/kg/day or less (USEPA, 2008a). This is 1% of the ENVIRON RfD of 25 µg/kg/day. Thus, with 99% of the total perchlorate dose allowable in drinking water, an RSC of 0.99 was applied to the RfD to calculate an acceptable drinking water level.

The representative body weight and daily drinking water ingestion rate used in the drinking water calculation were taken from the USEPAs *Estimated Per Capita Water Ingestion and Body Weight in the United States – An Update* (USEPA, 2004). For pregnant women, 50% percentile for body weight was 63 kg, while the 95th percentile for daily drinking water ingestion rate was 2.5 L/day, respectively (USEPA, 2004). These are conservative choices, assuming higher drinking water (and perchlorate) ingestion than the majority of pregnant women.

Using the values discussed above, an acceptable drinking water level was calculated as:

$$acceptable\ drinking\ water\ level\ (\mu g/L) = \frac{\frac{BMDL}{UF} \times RSC \times BW}{IR}$$

$$acceptable\ drinking\ water\ level\ (\mu g/L) = \frac{\frac{250\ \mu g/kg/day}{10} \times 0.99 \times 63kg}{2.5\ L/day}$$

$$acceptable\ drinking\ water\ level\ (\mu g/L) = 620\ =\ 620 \text{ parts per billion}$$

The proposed acceptable drinking water level of 620 µg/L is 2-3 orders of magnitude higher than the federal and state drinking water advisory and standards for perchlorate. The reason for the marked difference in the proposed drinking water level and those of Cal EPA, Mass DEP, and USEPA is the choice of study and critical endpoint. The published data for humans, including iodine-deficient pregnant women and their infants, support the choice of subclinical hypothyroidism (an adverse effect) as the critical effect, rather than RAUI, a non-adverse effect which has been shown to occur in the absence of any adverse effects on human growth, development, or metabolism (Braverman et al., 2004; Tellez et al. 2005; Buffler et al. 2006; Cao et al. 2010; Pearce et al. 2010, 2011). The proposed value was calculated based on conservative parameter value choices, including a BMDL modeled using a conservative threshold for thyroid hormone response, addition of an UF of 10 (assuming existence of perchlorate-sensitive subpopulations), and an assumed high drinking water ingestion rate (95th percentile for pregnant women).

4 Summary and Conclusions

The weight-of-evidence from the human clinical, occupational, and epidemiological data does not support the hypothesis that perchlorate in drinking water has resulted in adverse effects, including subclinical hypothyroidism, even in subpopulations that are presumed by others to be more sensitive to changes in thyroid iodide uptake. The critical endpoint on which the proposed drinking water level is based is the potential for subclinical hypothyroidism, as would be indicated by decreased blood T_4 concentration and/or increased blood TSH concentration. Changes or lack thereof in thyroid hormone levels is a more appropriate biomarker for potential effects on the thyroid. Inhibition of iodide uptake is not the appropriate endpoint for toxicity assessment in humans because of the ability of the thyroid hormone system to adapt to transient changes because of normally functioning compensatory, feedback, and homeostatic mechanisms. Thus, inhibition of iodide uptake is not necessarily an indicator of impending downstream toxicity at exposure levels in which thyroid hormone levels are maintained without overstressing the compensatory mechanisms. The human data discussed previously and in the Appendix provide strong evidence that normal thyroid hormone function can be maintained during chronic exposures to perchlorate that may also cause inhibition of iodide uptake in adults (Lamm et al., 1999; Braverman et al., 2004; Tellez et al. 2005; Pearce et al. 2010, 2011;) and newborn infants (Buffler et al. 2006; Cao et al. 2010) but without indications of adverse changes in thyroid hormone levels or thyroid function.

The proposed acceptable perchlorate drinking water level of 620 µg/L differs from the USEPA, Cal EPA, and Mass DEP values of 2-15 µg/L because of the selection of subclinical hypothyroidism as the critical endpoint, rather than inhibition of thyroidal iodide uptake, and because of the relatively small contribution that dietary perchlorate likely makes to the allowable daily dose. The proposed value is preferable to the existing regulatory values because it takes into account non-adverse compensatory mechanisms of thyroid biology, is based on observations of chronic exposure, and protects against an adverse, versus non-adverse, effect.

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Appendix A

A.1 Thyroid Biology and Function

Thyroid hormones leave the thyroid, circulate throughout the bloodstream, and enter and interact with organ systems throughout the body. Thyroid hormones are thyroxine (T_4) and triiodothyronine (T_3). Thyroxine is produced in the thyroid and then, with assistance of specific enzymes produced in the liver, convert to T_3. The thyroid uses specific proteins (called sodium-iodide symporters, or NIS) found on the surface of thyroid cells (thyroid follicles) to actively take iodine from the blood. The NIS molecules are the targets of perchlorate, with inhibition of iodide uptake demonstrated in short-term volunteer data (Greer et al., 2002) or long-term therapeutic use (discussed below). Other proteins within the thyroid follicles, along with a hormone from the pituitary gland (thyrotropin, or TSH), integrates the iodine into the formation of T_3 and T_4 molecules. In humans, the thyroid can store significant quantities of T_3 and T_4 in the thyroid cells.

In the cells of the body, T_3 is the active thyroid hormone that interacts with specific molecules in the cell, including portions of DNA, to turn on and off processes that initiate, increase, or decrease growth, development, and energy metabolism. T_4 has little, if any, biological function itself; it is at the ready when needed to be transformed within the cells into T_3 by the removal of one iodine atom. The liberated iodine atom re-enters the circulation where it can be taken back up into the thyroid and re-cycled into new T_3 or T_4, or it may be eliminated in the urine or, to a lesser extent, the saliva and breast milk. Iodine has no other known function in the human body.

In humans and other mammals, most of the thyroid hormone in the blood is in the form of T_4. Further, over 99% of T_4 and T_3 in human blood is bound to specific proteins to act as a ready source of thyroid hormone. As free, unbound T_3 and T_4 are taken from the circulation into body tissues, it is replaced by release of bound hormone. Thus, the body maintains a constant, low level of free T_3 and T_4 in the blood. This capability of healthy humans to maintain a ready supply of thyroid hormone bound in the blood as well as stored in the thyroid itself is not present in laboratory rodents. In rats, the thyroid is constantly stimulated to maintain adequate T_3 and T_4 levels in the circulation. Thus, rats are more susceptible than humans to effects arising from subtle changes in thyroid function and thyroid hormone levels. This difference between species is important when comparing the effects of perchlorate, or any other thyroid-acting agent, in humans and laboratory animals, as is discussed below in greater detail.

Mechanisms are at work in the human body to precisely maintain adequate levels of thyroid hormone in the blood as needs change. The pituitary gland located in the brain can stimulate the thyroid to increase production of thyroid hormone should blood levels of T_4 decrease. Falling T_4 levels in the blood signal the hypothalamus, a specialized region of the brain, to secrete a hormone, TRH, which signals the pituitary to begin secretion of TSH, which stimulates

a number of functions in the thyroid, including increasing the capacity for iodine uptake (through increasing the number of NIS molecules on the thyroid cell surfaces), increasing the production of T_3 and T_4, and increasing production of special proteins that bind T_4 in the blood. Adequate blood T_4 levels signal the hypothalamus and pituitary gland to stop production of TRH and TSH, respectively, which halts the stimulation of the thyroid. This tightly controlled set of feedback and feed-forward mechanisms is known collectively as the hypothalamus-pituitary-thyroid axis.

If conditions occur such that T_4 levels in the blood are too low to maintain proper regulation of growth, development, or metabolism, a medical condition known as hypothyroidism results. Hypothyroidism has numerous causes, including autoimmune thyroid disease, congenital abnormalities of thyroid or pituitary function, treatment with iodine-containing drugs or radiographic contrast agents, or iodine deficiency in the diet. Hypothyroidism can be further graded as subclinical, mild, or overt indicated by slight, moderate, or high levels of TSH in blood and, for mild or overt cases, low blood T_4 levels (Ross, 2005).

A.2 Toxicity Data for Perchlorate

According to the animal and human data discussed below, perchlorate at high doses inhibits the uptake of iodine by NIS proteins on the surface of thyroid follicle cells, thereby, inhibiting the transport of iodine into the thyroid cell. However, the magnitude and duration of reduced iodide uptake into the thyroid must be high enough to overcome compensatory mechanisms that act to maintain homeostatic control to sustain normal thyroid function. One of the ways that the hypothalamus-pituitary-thyroid axis compensates for reduced thyroid uptake is to stimulate an increase in the number of NIS proteins, resulting in more entry points for iodine and reducing the inhibitory effect of perchlorate. Studies in humans have shown that, while perchlorate exposure can result in inhibition of iodide uptake in the short term (Greer et al., 2002), there are transient and adaptive homeostatic mechanisms to offset in humans increases in iodine uptake (Braverman et al., 2004, 2006). This capability can be overwhelmed (as in the case of therapeutic uses of high doses of perchlorate), but at environmental levels of perchlorate exposure, decreased T_4 in the blood does not necessarily follow inhibition of iodide uptake into the thyroid.

The scientific literature for perchlorate toxicology includes many studies in laboratory animals and humans, which are summarized below. Human studies are preferred to determine the dose-response of any chemical. Data from animal studies in the appropriate species should be reviewed as well, bearing in mind the physiological differences between species. As is discussed below, perchlorate interacts similarly with the NIS molecules in human and animal thyroid cells, but the resulting changes in available iodide and resulting levels of thyroid hormone in the circulation are very different between laboratory rodents and humans.

A.2.1 Summary of Human Data

A.2.1.1 Clinical Uses for Perchlorate in the Treatment of Hyperthyroidism

In the 1950s and 1960s in patients with hyperthyroidism, potassium perchlorate was administered to inhibit thyroid iodide uptake, thus reducing the production of T_4 and T_3. Administration of potassium perchlorate was typically at doses ranging from 400 to 2000 mg/day for several weeks or months disease (Leung et al., 2010). Few side effects were noted in these

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patients, with the frequency of side effects reported increasing with increasing dose. However, because of the observation of some side effects and the development of better anti-thyroid drugs, the use of perchlorate to treat hyperthyroidism ceased by the late 1960s.

Although not used as frequently, perchlorate is still used today diagnostically to detect defects in the synthesis of thyroid hormones (NRC 2005). It is also used specifically to treat hyperthyroidism resulting from the administration of the anti-arrhythmic drug, amiodarone. While perchlorate continues to be used for these specific applications, the Food and Drug Administration does not recognize perchlorate as a pharmaceutical for the treatment of endocrine or metabolic disorders (NRC 2005).

A.2.1.2 Occupational Studies

Several occupational studies have been conducted to evaluate thyroid function in workers following long-term exposure to ammonium perchlorate (Gibbs et al. 1998; Lamm et al. 1999; Braverman et al. 2005). Regardless of the characterization of exposure in these cohorts (estimated daily doses approximately 0.3 mg/kg/day), no significant association between estimated exposure to perchlorate and alterations in any of thyroid hormone or TSH measures was reported. In the Gibbs et al. (1998) study, only duration of shift was related to changes in TSH concentrations, with this observation possibly being associated with an increase in serum TSH concentrations expected for workers' changes in the day/night cycle.

The only significant change in an endpoint related to thyroid function reported in any of the occupational studies, was a significant decrease in thyroid radioactive iodine uptake (RAIU) reported in workers following three 12-hour shifts compared to pre-exposure measurements (Braverman et al., 2004). However, serum TSH, serum thyroglobulin (Tg) (a protein essential for thyroid hormone formation) and thyroid volume were not affected. In addition, the RAIU measured in workers during exposure, while lower than preshift values, was comparable to those of community controls. These findings indicated a compensatory response to inhibition of iodide uptake occurring early on in every 3-day work shift, but not result in adaptive changes seen in adults that would result in the development of hypothyroidism or goiter.

A.2.1.3 Ecological Epidemiology Studies

Ecological epidemiology studies have been conducted examining possible associations between environmental exposure to perchlorate in drinking water (4-120 µg/L) and various effects, including thyroid function, thyroid disease, and cancer in children (including low-birth-weight or preterm newborns and offspring of mothers who were hypothyroid or had iodide deficiency during gestation) and adults (Rockette and Arena, 1983; Li et al., 2000a, 2000b, 2001; Morgan and Cassidy, 2002; Lamm and Doemland, 1999; Brechner et al., 2000; Crump et al., 2000; Schwartz et al., 2001; Chang et al., 2003; Kelsh et al., 2003; Lamm, 2003; Buffler et al., 2004, as cited by NRC 2005). NRC (2005) noted that while ecologic study design may be limited in their ability to establish cause-and-effect of toxicity, the association, or lack thereof, of exposure and toxic endpoint can be informative when combined with other data on the biology of the thyroid gland and experimental studies of the effects of acute exposure to perchlorate. The NRC Committee concluded that the available epidemiologic data did not indicate a causal association between perchlorate exposure and congenital hypothyroidism, perturbations of

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thyroid hormone and TSH production in normal newborns, or thyroid diseases or hypothyroidism in normal adults. NRC (2005) further determined that there was inadequate evidence to motivate the conduct of a study of possible associations between perchlorate exposure and neurodevelopmental outcomes in children (e.g., autism, ADHD) or thyroid cancer in adults.

Ecological epidemiological studies published since the NRC (2005) assessment have focused on evaluating the potential association between perchlorate exposure and indicators of thyroid function in pregnant women (Pearce et al. 2010, 2011; Tellez et al. 2005) and newborn infants (Buffler et al. 2006; Cao et al. 2010). In the Pearce et al. (2010) study, subjects were a subset of pregnant women involved in the Controlled Antenatal Thyroid Screening Study (CATS). This prospective study was designed to determine whether L-T_4 for hypothyroid or hypothyroxemic pregnant women during pregnancy improves child development. In 2002, a total of 22,000 women with single pregnancies at less than 16 weeks were enrolled in this program. For the subset 1002 women considered by Pearce et al. (2010), urinary iodine, thiocyanate, and perchlorate and serum TSH, free T_4 and thyroperoxidase antibodies (an indicator of thyroid function) were measured. Urine perchlorate was detectable in all women studied, with a median concentration of 2-5 µg/L, depending upon location (Turin, Italy versus Cardiff, Wales). No associations between urine perchlorate concentrations and serum TSH or free T_4 were observed. In addition, perchlorate in urine was not a predictor of free T_4 or TSH in blood. The authors concluded that low-level perchlorate exposure is ubiquitous, but it is not associated with alterations in thyroid function among iodine-deficient women in the first trimester of pregnancy. They also noted that their sample is the largest to date in women with low urinary iodine levels, all of whom were pregnant, and that it is in contrast to a smaller study conducted in the United States by Blount et al. (2006). Pearce et al. (2011) reported similar results in a study conducted in smaller groups of pregnant women from Los Angeles, California (N=134) and Cordoba, Argentina (N=107). In nonpregnant women with similar urine iodine (less than 100 µg/L) and perchlorate concentrations as those reported by Pearce et al. (2010), Blount et al. (2006) reported increases in serum TSH and lower serum T_4 concentrations. However, a re-analysis of the same data by Pearce et al. (2007) in which urinary perchlorate levels were more appropriately corrected for creatinine excretion (reducing the effect of variable urine volume among subjects), did not find an association urinary perchlorate and T_4 and TSH levels in blood.

Tellez et al. (2005) conducted a longitudinal epidemiological study among pregnant women in three areas of Chile with drinking water concentrations of perchlorate that varied from 0.5 to 114 µg/L. It was the same areas evaluated by Crump et al. (2000) to evaluate potential effects in school children from exposure to perchlorate. No increases in thyroglobulin (Tg) or TSH or decreases in free T_4 were observed among women in early pregnancy (approximately 16 weeks) or late pregnancy (approximately 32 weeks). In addition, no significant changes in the thyroid hormone indicators were seen in newborns related to perchlorate drinking water concentration. These studies have been criticized for focusing on a population having higher iodine ingestion than in the U.S. Further analysis, however, by Van Landingham and Gibbs (2008) of only iodide-deficient women within these data found no association between urinary perchlorate and T_4 or TSH levels.

In ecologic studies focused on the evaluation of indicators of thyroid function in infants (Cao et al. 2010; Buffler et al. 2006), Cao et al. (2010) reported a weak but significant association

between higher urinary perchlorate (expressed as log perchlorate in µg/g creatinine) and higher TSH concentrations in infants with lower urinary iodine (<100 µg/L) in children enrolled in the Study of Estrogen Activity and Development (Cao et al. 2009). This study design was partly cross-sectional (offering a "snapshot" of data in time) and partly longitudinal (following the subjects over time), since some children were evaluated at multiple visits. Blood and urinary TSH and T_4 were measured in each child at each visit.

The Buffler et al. (2006) study included 342,257 newborns screened by the California Newborn Screening program in 1998, whose mothers resided in communities in which ground water was tested for perchlorate in 1997 or 1998. The endpoints of interest for evaluation in the study were the presence of clinically-diagnosed primary congenital hypothyroidism (PCH) and serum TSH concentrations in the newborns. In evaluating any correlation TSH and perchlorate ground water concentrations, the authors considered the time in which perchlorate was measured in the infant after birth as a critical factor in evaluating the results, because a normal postnatal surge of TSH is present within the first 24 hours after birth that could impact the interpretation of the results. Therefore, only infants whose TSH was measured at a time point greater than or equal to 24 hours of age was considered. Calculations were controlled for confounding factors such as sex, ethnicity, birth weight, and multiple birth status. The study authors reported no association between estimated average perchlorate concentrations of greater than 5 µg/L in drinking water supplies and the prevalence of clinically diagnosed PCH or high TSH concentrations.

A.2.1.4 Clinical Volunteer Studies

Several clinical studies have been conducted to evaluate the potential effects of potassium perchlorate in healthy subjects, with exposure duration ranging from 2 weeks to 6 months (Brabant et al. 1992; Lawrence et al. 2000, 2001; Greer et al. 2002; Braverman et al. 2006). Doses in these studies ranged from 0.007 to 0.5 mg/kg/day in drinking water. Endpoints considered in these studies included measurements of serum T_4, T_3, and TSH concentrations, as well as evaluation of changes in RAIU.

No statistically significant changes in thyroid hormone levels (T_4, T_3, TSH levels in blood) that would indicate an impact on thyroid function leading to hypothyroidism were reported in any of these clinical studies. Some authors noted slight decreases in TSH (Brabant et al. 1992; Greer et al. 2002), which is inconsistent with hypothyroidism, in which a significant increase in TSH would be expected. Significant transient decreases in 24-hour RAIU were noted in clinical studies in which perchlorate was administered for 2 weeks, with a return to baseline levels following cessation of exposure (Lawrence et al. 2000, 2001; Greer et al. 2002). However, most importantly, in the study with the longest duration of exposure (6 months) (Braverman et al. 2006), no statistically significant effect on 24-hour RAIU was observed. While this study is limited by small sample size (N=13, 9 treated and 4 placebo controls), it does provide information on levels of perchlorate ingestion (up to approximately 0.04 mg/kg/day) to which healthy individuals can be exposed for a longer-term duration with no impact on indices of thyroid function.

USEPA (2005) based the current Reference Dose (RfD) on changes in RAIU uptake reported in the 2week clinical study by Greer et al. (2002), which provided evidence that there were no

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other significant changes in T_4, T_3 and TSH concentrations. USEPA (2005) also noted that chronic exposure will have no greater effect than that resulting from short term exposure; lack of the precursor event of inhibition of iodide uptake will result in no changes in thyroid function in the short or long term. In fact, prolonged exposure will actually have less effect because of the capacity of the hypothalamus-pituitary-thyroid axis to compensate for iodide deficiency by increasing iodide uptake, as seen in the Braverman et al. (2005) study of perchlorate workers. USEPA (2005) further noted that if some inhibition of iodide uptake by the thyroid did occur at the minimal dose at the point of departure, data from humans indicated that longer exposures were not likely to result in a greater or more severe response.

A.2.2 Summary of Laboratory Animal Data

The following sections include a brief review of the animal studies pertaining to perchlorate health effects. The studies evaluated for these sections were those included in the NRC (2005), *Health Implications of Perchlorate Ingestion* report and those studies, published post-2005 located in a literature review. The information summarized in this section includes results of rodent studies that look for changes in thyroid hormone levels, reproductive and developmental effects, brain changes, and cancer.

A.2.2.1 Effects on Thyroid Hormone Levels

An evaluation of the effects of perchlorate on thyroid hormones and thyroid histopathology was conducted in pregnant rats and their offspring (Argus, 2001; York et al., 2001a). Argus (2001) gave pregnant rats perchlorate in drinking water at doses ranging from 0.01 to 30 mg/kg/day throughout pregnancy (gestation) and lactation. Argus (2001) reported dose-related increases in serum TSH in the mothers (dams), fetuses, and pups at ≥0.01 mg/kg/day, decreases in T_4 at ≥0.01 mg/kg/day, and decreases in T_3 at 30 mg/kg/day. The NRC (2005) summary of the Argus (2001) study did not indicate whether statistical analyses used individual pups or litters as the experimental unit for comparison of thyroid hormone levels. Similar significant decreases in T_4 were also reported in pregnant rabbits at doses ≥30/mg/kg/day (York et al. 2001b).

Studies in non-pregnant rats or pregnant prairie voles (James-Walke et al., 2006) and deer mice (Smith et al., 2006) did not report changes in thyroid hormone levels. Drinking water concentrations that resulted in an estimated intake of perchlorate of 0.05 or 0.4 mg/kg/day for 21 days did not produce significant changes in blood T_4 hormone levels in female rats (James-Walke et al. 2006). Similar results were reported in prairie voles and deer mice given perchlorate at concentrations resulting in 0.7-1.1 mg/kg/day in either food or drinking water (Smith et al. 2006).

Two studies in rats have investigated the effects of iodide deficiency on the thyroidal effects of perchlorate exposure(Paulus et al., 2007; Wu et al., 2010). Rats fed iodine-deficient diets absorbed greater amounts of iodide into the thyroid at about twice the rate of rats fed normal diets (Paulus et al. 2007). Following administration of perchlorate at concentrations of 1.1-28 µg/L in drinking water (0.1-3 mg/kg/day), the normal-diet rats showed significant inhibition of thyroidal iodide uptake at all doses, while the iodide-deficient rats had significant inhibition of iodide uptake only at 28 µg/L. These findings indicated that iodide-deficiency in rats stimulates

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a compensatory increase in iodide uptake capacity that offsets perchlorate-induced inhibition up to a certain level.

Wu et al. (2010 reported similar reductions in T_4 and increases in TSH in treated and in non-treated iodine-deficient rats. They also reported differences in genetic expression of two enzymes and proteins involved with T_3 and T_4 production in the thyroid at different doses, but not in the iodine-deficient animals. These study authors speculated that, in addition to iodide uptake inhibition, perchlorate may affect thyroid hormone balance by another mechanism. However, they offered no explanation as to why the differences in genetic expression markers were not expressed at the same levels that affected T_4 and TSH, or why iodine deficiency resulted in similar changes to T_4 and TSH if there were, in fact, another mechanism responsible to effects associated with perchlorate exposure in laboratory rats.

McLanahan et al. (2009) used a mathematical computer model to investigate the influence of iodine uptake inhibition on thyroid hormone levels. Their results corroborated the conclusions of Wu et al. (2010), suggesting that the effects of perchlorate in the thyroid may to occur through more thanone mode of action, by blocking iodide transport as well as interacting in some way with thyroid hormone production and release.

A.2.2.2 Effects on Brain Structure

Argus (1998) reported an increase in thickness of specific brain tissues of rat pups born to dams exposed 0.1-10 mg/kg/day perchlorate in drinking water throughout pregnancy. Argus (2001) extended their 1998 analysis by performing brain measurements on additional groups of rats using a higher dose (30 mg/kg/day) and additional sampling times during pregnancy. Again, they reported significant increases in thickness of brain tissues, but could not demonstrate an increase in effect as doses increased.

Concerns have been raised about the Argus (1998, 2001) studies from outside reviewers (Harry, 2001; Wahlsten, 2002; Elberger, 2003; Gellar, 2003). In general, the concerns were: 1) The systematic differences in how brain samples were measured between treatment groups; 2) the lack of a dose-response relationship, and 3) concerns about the biologic plausibility of the changes that were reported. Based on their review of Argus (1998, 2001), NRC (2005) concluded that the data from Argus (1998, 2001) were inadequate to identify a causal relationship between maternal perchlorate exposure and pup neurodevelopmental abnormalities.

A.2.2.3 Effects on Neurobehavior

Previous research has suggested that changes in thyroid hormone levels occurring during fetal development could interfere with normal brain development, including changes in the brain areas that may be involved in motor coordination (Chan and Kilby, 2000). The Argus (1998) study discussed above included a battery of behavioral tests performed on the offspring of rats exposed to perchlorate in drinking water during pregnancy. Significant changes were not observed during several standard tests following doses of 0.1 to 3 mg/kg/day, the highest dose tested. However, Argus (1998), but not Bekkedal et al. (2000), observed significant changes in locomotor activity in litters of rat pups born to dams exposed to 10 mg/kg/day.

The effects of perchlorate on developmental neurotoxicity reported by Argus (1998) were not observed in a longer exposure study by York et al. (2005a, 2005b). Offspring from female rats exposed to up to 30 mg/kg/day perchlorate from 2 weeks prior to mating through day 10 of lactation exhibited no changes in a variety of motor activity variables, suggesting that perchlorate exposure in the womb and through lactation did not significantly affect the development of simple muscle movements in pups (York et al., 2005b).

Exposure to perchlorate during gestation did not impair behavioral test endpoints in the male offspring of females exposed to drinking water concentrations up to 1000 ppm (Gilbert and Sui, 2008). Significant reductions in electrophysiological assessments (suggesting adverse effects in the hippocampal region of the developing brain) were reported for the offspring at all dose levels. However, a consistent dose-response relationship was not observed, and the lack of behavioral changes (sensitive to deficiencies in the brain hippocampus) did not comport with measured electrophysiological changes (Mavis and DeSesso, 2009).

To evaluate the thyroid hormone action in the brain, Sharlin et al. (2010) measured gene expression, indicators of thyroid hormone action in the brain, in the offspring of pregnant rats administered methimazole and potassium perchlorate to induce hyperthyroidism during gestation. There was a significant decrease in blood T_4 levels and body weight in young pups. However, the findings did not support the notion of the developing rat brain being capable of compensating for low T_4 levels.

A.2.2.4 Effects on Reproductive and/or Developmental Function

Studies in several species examined the effect of perchlorate exposure in the diet or drinking water on reproduction. No changes in reproductive endpoints were see in rats (York et al. (2005a, 2005b), deer mice or prairie voles (Smith et al., 2006), or rabbits (York et al., 2001b).

A.2.2.5 Thyroid Gland Tumors

Cancer and noncancer effects on the thyroid gland have been reported in both mice and rats following long term exposures to high doses of perchlorate (Kessler and Kruskemper, 1966; Pajer and Kalisnik, 1991; Fernandez-Rodriguez, 1991). Thyroid cellular changes and nodules were reported in female rats administered 1% perchlorate in drinking water for up to 12 months (Fernandez-Rodriguez, 1991). In rats, daily drinking water doses of 1,339 mg/kg/day for a lifetime produced benign thyroid tumors in 4 of 11 treated rats (Kessler and Kruskemper, 1966), while thyroid carcinomas were observed in 5 of 6 mice exposed to 2,147 mg/kg/day in drinking water for 46 weeks (Pajer and Kalisnik, 1991). In both studies of mice and rats, no tumors were observed in the control animals.

Thyroid benign tumors were reported in male rats in a two-generation reproductive study (Argus 1999). In this study, male rats in the first generation were given perchlorate in drinking water from 70 days before mating until age of 24-25 weeks. The male offspring were exposed to the same duration of dosing, with additional exposure through pregnancy and lactation. The microscopic tissue changes, which were re-evaluated by USEPA (Wolf, 2000; USEPA, 2002), reported that two first-generation males in the 30 mg/kg/day group and one second-generation male control rat had benign thyroid tumors. Both the USEPA (2002) and the NRC (2005) concluded that while the thyroid tumors seen in the treated male rats were not statistically

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significant, the appearance of tumors as early as week 19 indicated that they were likely treatment-related.

A.3 Differences in Animal and Human Perchlorate Toxicokinetics

The function of the thyroid in rats and humans is qualitatively similar; however, some differences between the two species in chemical binding of perchlorate to thyroid proteins in the blood and rates of clearance from the body present important quantitative differences (NRC 2005). The principal protein that binds T_4 in human, thyroxine-binding globulin (TBG) is not present in rats. Most of the T_4 in rats is bound to two other bold proteins: albumin and transthyretin, which have a T_4 binding affinity ("tightness of binding") of about 100 times less than TBG in humans. Therefore, T_4 is cleared from the body more quickly in rats than in humans, requiring a higher production rate of T_4 per unit body weight. In the liver, rats and humans join T_4 to a specific carbohydrate molecule to form a compound class (glucuronide conjugate) that may then be eliminated in the bile. This mechanism is used by the body to promote elimination of many chemicals. However, about 50% of T_4 in the rat gets eliminated in the bile, compared to only 10-15% in humans.

The lower binding capacity for T_4 blood as well as the much smaller thyroidal storage capacity of T_3 and T_4 in rats, compared to human, requires that rats produced thyroid hormone on a continual basis, with almost constant stimulation by TSH. In studies of perchlorate-induced iodide uptake inhibition, rats exhibited compensation for reduced iodide availability within 5 days (York et al., 2002) of exposure, while human volunteers did not compensate by 14 days of drinking water exposure, even though iodide uptake was inhibited by as much as 67% (Greer at al., 2002). Longer durations of perchlorate exposure in human volunteers (6 months) (Braverman et al., 2006) and perchlorate workers (≥1.7 years) (Braverman et al., 2004) did result in evidence for compensatory mechanisms by increasing the thyroid's capacity to take up iodide from the blood.

Changes in blood concentrations of T_3, T_4, and TSH following perchlorate exposure are different in rats and humans. Following 14 days of perchlorate exposure in rats, Siglin et al. (2000) reported significant decreases in T_3 and T_4 levels, and significant increases in TSH. However, no significant changes in TSH, T_3, or T_4 have been reported in adult humans exposed to up to 0.5 mg/kg/day perchlorate for 14 days (Lawrence et al. 2000; Greer et al. 2002), six months (Braverman et al., 2004), or ≥1.7 years (Lamm et al., 1999; Braverman et al., 2004).

There are also differences between rats and humans in pituitary-thyroid function during pregnancy and in the fetal development of the thyroid. In humans, blood T_3 and T_4 levels increase during pregnancy and remain elevated through most of pregnancy (Glinoer 1997). In rats, blood T_4 levels significantly decrease during gestation days 17-22 (4 days leading up to birth), compared to non-pregnant rats (Fukuda et al. 1980; Calvo et al. 1990; Versloot et al. 1994). These differences are mostly related to the lack of TBG in rats. At birth, thyroid function in the rat is relatively immature, and equivalent to that of a third-trimester human fetus. In humans, thyroid function in the womb supported by maternal thyroid hormones, while T_4 and T_3 levels in newborn rats don't increase until 5 to 15 days after birth due to an increase in a blood thyroid hormone binding protein (Obregon et al. 1991).

Computer models capable of simulating perchlorate toxicokinetics in rats and humans, termed physiologically based pharmacokinetic (PBPK) models, have been developed (Clewell et al., 2007) and evaluated by USEPA (2009). These models allow for prediction of perchlorate doses to various tissues, including transfer of perchlorate and iodide to the developing fetus and breastfeeding infant, under a variety of exposure scenarios. However, the models were not designed to predict compensation of the hypothalamus-pituitary-thyroid axis for inhibited RAIU or the effect that these mechanism have on thyroid hormone levels. Because of this, the models are limited in their application to simulate and compare chronic doses and effects (or lack) reported in occupational or epidemiological studies.

A.4 Relevance of Animal Data to Human Risk

With regard to non-cancer and cancer effects of perchlorate, the rodent data should not be used in the quantitative estimation of human risk. Comparison of differences between the species of the physiology of the of the thyroid gland, capacity of thyroid hormone binding in blood, rate of elimination from the system, and onset of hormone production and availability of maternal hormones in the developing offspring indicate that rats are clearly more sensitive than humans to perturbations of iodide uptake into the thyroid. Because the rat thyroid is under near-constant stimulation by the pituitary gland to maintain blood T_4 levels, not having the reserve of thyroid hormone in the thyroid and the blood found in humans, additional chemical-induced stresses on the hypothalamus-pituitary-thyroid axis are likelihood to result in adverse effects not seen in humans or at much lower doses and shorter exposure durations (USEPA, 1998).

For thyroid carcinogenicity, an International Agency for Research on Cancer (IARC) working group stated that chemicals found to induce thyroid tumors in rodents by interfering with thyroid hormone balance can, with some exceptions (i.e., sulfonamide drugs), also interfere with human thyroid balance if given long enough at sufficiently high doses. However, these agents can be assumed not to cause cancer in humans at exposure levels that do not lead to changes in human thyroid hormone balance (IARC, 2001). This was echoed in a USEPA science policy document (1989) and by NRC (2005), stating that humans may not be as sensitive quantitatively to thyroid cancer development of thyroid-pituitary disruption as are rodents.

Public Comments

Submitted By

American Chemistry Council

November 23, 2016

Mr. Russ Perkinson
U.S. EPA, Office of Ground Water and Drinking Water
Standards and Risk Management Division
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Submitted via the Federal eRulemaking Portal: http://www.regulations.gov

Re: Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate, Docket No. EPA-HQ-OW-2016-0438-0001 (81 Federal Register 67350, September 30, 2016)

Dear Mr. Perkinson:

The American Chemistry Council[1] (ACC) is pleased to submit these comments on EPA's proposed Peer Review Materials to Inform the Safe Drinking Water Act Decision Making on Perchlorate,[2] specifically the draft Biologically Based Dose-Response (BBDR) Model and the accompanying draft model report titled "Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses."[3] ACC supports the use of the best available science to support regulatory actions for perchlorate, one of the most well-studied drinking water contaminants[4] with detailed information on the mode of action, dose-response, and health effects.

[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $797 billion enterprise and a key element of the nation's economy. It is the largest exporting sector in the U.S., accounting for 14 percent of U.S. exports. Chemistry companies are among the largest investors in research and development, investing $93 billion in 2015.
[2] 81 Federal Register 67350–67351.
[3] EPA (Schlosser et al.). 2016.
[4] See Cotruvo, J. 2015. Perchlorate in US Drinking Water: Is a Federal Regulation Needed to Protect Public Health? *Journal AWWA*, 107(6):66–71.

Support for Modeling Approach
In 2013, EPA's Scientific Advisory Board (SAB) panel recommended that EPA develop a physiologically-based pharmacokinetic/pharmacodynamics (PBPK/PD) modeling approach to support the development of a National Primary Drinking Water Regulation (NPDWR) for perchlorate.[5] ACC continues to support EPA's commitment to derive a maximum contaminant level goal (MCLG) for perchlorate using BBDR modeling and mode of action information rather than the default MCLG ("algebraic") approach using the reference dose (RfD) and specific chemical exposure parameters and associated assumptions.[6] In response to SAB, EPA, working with U.S. Food and Drug Administration (FDA) scientists, developed a draft BBDR (also called PBPK) model that integrates PBPK/PD models for perchlorate and iodide with BBDR models for thyroid hormones. The integrated model predicts the effect of perchlorate on thyroid hormone levels in lactating mothers, as well in formula- and breast-fed infants.

Sensitive Subpopulations
While EPA's focus on one or more of these sensitive populations is appropriate, its potential selection of a nutritionally iodine-deficient subpopulation of these sensitive populations as the basis of its BBDR modeling—and subsequent development of an NPDWR—would be unprecedented.

> **Recommendation – At a minimum, EPA should acknowledge both the exceptionally conservative nature of the approach and that its use should correspond with a reduction in or elimination of the use of uncertainty factors in the subsequent development of an MCLG.**

Hypothyroxinemia and the Critical Effect
The integrated draft model focuses on "hypothyroxinemia"—a condition that occurs when free thyroxine (fT4) levels are decreased while thyroid-stimulating hormone (TSH) levels are maintained in the normal range—as an indicator of potential adverse health effects resulting from exposure to perchlorate. Hypothyroxinemia is considered a more sensitive and therefore better "indicator of the potential adverse health effects than the more pronounced decreases in thyroid function associated with hypothyroidism".[7] However, the selection of hypothyroxinemia is not consistent with EPA's definition of "critical effect"—that is, the first adverse effect or its known precursor [singular] that occurs as dose rate increases.[8] There is no clinical definition of hypothyroxinemia and it is not characterized as adverse or treated by medical authorities. Rather, its mode of action is unknown and might be adaptive or compensatory—neither of which is adverse. Also, no clear fT4

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[5] EPA SAB. 2013. SAB Advice of Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004 (dated May 29, 2013).
[6] ACC letters to EPA DFO Mr. Thomas Carpenter regarding EPA's SAB Perchlorate Advisory Panel activities dated July 9, 2012, September 20, 2012, and November 29, 2012.
[7] EPA (Schlosser et al.). 2016, p. 6, lines 8–10.
[8] EPA. 2016. Integrated Risk Information System (IRIS) Glossary/critical effect.

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reference range exists in the literature to define it. According to the National Research Council's seminal review of perchlorate[9] and EPA's definition, the critical effect is hypothyroidism or its immediate precursor, thyroid hypertrophy or hyperplasia.

> **Recommendation – EPA should provide additional justification for using hypothyroxinemia as the critical endpoint for determining adverse effects associated with perchlorate exposure.**

Model Parameters and Validation

Although the proposed BBDR model uses multiple physiological parameters (e.g., body weight over time, fractional blood flow) to set the life-stage-specific values for iodide/thyroid hormones and perchlorate, EPA's draft model report notes that "many of the iodide/thyroid hormone and perchlorate parameters where [sic] not available for specific life-stages, and so were extrapolated from other life-stages or in-vitro data".[10] Therefore, assumptions have been made to set the parameters for the model that might weaken the predictive outcomes of the draft model.

> **Recommendation – EPA should carefully consider any deviations between its draft model output and observations from available prospective epidemiology studies such as Téllez et al. (2005).[11]**

Moreover, if appropriate data are not available to validate the model (i.e., "back-check" modeling results with observations) additional data will need to be collected from biomonitoring studies or generated in animals before the model can be considered to accurately predict outcomes resulting from exposure to perchlorate in drinking water.

The proposed BBDR model does not account for other chemicals besides perchlorate that also inhibit the sodium iodide symporter (NIS) that transports iodine into the thyroid,[12] such as nitrate and thiocyanate that form part of a healthy diet and that occur in background levels far exceeding perchlorate. The draft model also does not account for well-understood compensatory (homeostatic) control mechanisms that mobilize stores of iodine from the mother in the infant's thyroid.[13, 14] These stores compensate for short-term fluctuations in iodide uptake via NIS upregulation. If such upregulation is not addressed in the model, the results may contribute to an unduly conservative RfD/MCLG.

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[9] National Research Council. 2005. Health Implications of Perchlorate Ingestion. Washington, DC: National Academies Press.
[10] EPA (Schlosser et al.). 2016, p. 24, lines 7–9.
[11] Téllez, R., Michaud Chacón, P., Reyes Abarca, C., Blount, B.C., Van Landingham, C.B., Crump, K.S., and Gibbs, J.P. 2005. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. *Thyroid* 15:963–975.
[12] Agency for Toxic Substances and Disease Registry (ATSDR). 2008. Toxicological Profile for Perchlorates.
[13] Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2011. Perchlorate Evaluation.
[14] EPA Office of Inspector General. 2010. Scientific Analysis of Perchlorate. Report No. 10-P-0101.

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Peer Review

ACC commends EPA for forming two separate peer review panels to evaluate (1) the draft BBR model and draft model report, and (2) its application to develop a drinking water standard for perchlorate.[15] However, we still have concerns with several areas of the planned peer review process.

First, the companion Federal Register notice of September 30, 2016,[16] notes that EPA's contractor, Versar, Inc., will "provide a report to EPA summarizing the peer reviewer's [sic] evaluation of the scientific and technical merit of the draft model and draft report…" It is not clear that Versar, Inc. has the necessary expertise to accurately summarize the science and science policy questions and issues associated with the highly complex BBDR model or to accurately reflect the issues, conclusions, and recommendations of the peer review panel.

> **Recommendation – Given the complexity of the draft BBDR model and the 2013 SAB Perchlorate Panel's call for transparency, the planned peer review panel, not the contractor, should draft its own report to EPA.**

Second, the Federal Register notice also states that "Versar, Inc., will provide reviewers with a summary of public comments on the draft BBDR model and report submitted to EPA's docket..." Again, owing both to the complexity of the model and to adhere to the SAB Perchlorate Panel's call for transparency:

> **Recommendation – All public comments that are technical in nature should be provided directly to the peer review panel members in entirety—not just as a summary.**

Lastly, and consistent with the previous SAB panel process:

> **Recommendation – EPA's peer review process should result in a consensus-driven report rather than simply reflect the individual perspectives of the panel members.**

ACC appreciates consideration of these comments by EPA and the peer review panels. If you have any questions, please feel free to contact me by phone at 202-249-6709 or via email at judith_nordgren@americanchemistry.com.

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[15] ACC letter from Cal Dooley (President and CEO) to EPA Administrator Gina McCarthy dated June 20, 2016.
[16] 81 Federal Register 67347–67348.

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Sincerely,

Judith Nordgren

Judith Nordgren
Managing Director
Chlorine Chemistry Division

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Public Comments

Submitted By

American Water Works Association

American Water Works Association

Dedicated to the World's Most Important Resource®

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November 25, 2016

SUBMITTED VIA E-MAIL

Mr. Joel Beauvais
Deputy Assistant Administrator
USEPA, Office of Water
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

RE: Comments on the draft Biologically Based Dose-Response (BBDR) model for Perchlorate (81 FR 67350; EPA-HQ-OW-2016-0438)

Dear Mr. Beauvais:

The American Water Works Association (AWWA) appreciates the opportunity to review and comment on the draft Biologically Based Dose-Response (BBDR) model for Perchlorate (81 FR 67350; EPA-HQ-OW-2016-0438). Given the complexity of the model and originality of the approach, we believe that a 90 day comment period would have provided the public with a more reasonable opportunity for review and comment, but we appreciate the 11-day extension provided by the agency.

We also recognize and support EPA's work to address the recommendations made by the Science Advisory Board in 2013. In that regard, the following comments note several areas that we believe the peer review panel should evaluate closely and recommend actions that EPA can take to enhance the models scientific integrity. These comments are focused EPA's responsiveness to the model revisions recommended by the SAB and keys assumptions that the peer review panel should consider closly is assessing the efficacy of the model.

We recognize and support EPA's efforts to address the recommendations made by the Science Advisory Board in 2013. In that regard, the following comments note several areas that the peer review panel should evaluate closely. These include recommendations to enhance the model's scientific integrity, and comments on both EPA's responsiveness to the model revisions recommended by the SAB and on key assumptions in assessing the efficacy of the model.

In brief, our review found several assumptions that limit or constrain the models ability to reasonably generate biologically or clinically realistic outputs, especially when compared to prospective epidemiology studies. In addition, EPA's choice of critical effect requires careful review to ensure that EPA's own criteria are satisfied appropriately, especially since hypothyroxinemia is difficult to portray as a clinically relevant effect. Finally, a significant gap in the model is the absence of any consideration for the body's ability to up regulate the production of thyroid sodium-iodine symporter proteins. Such ability, already demonstrated with perchlorate exposure, makes any modeling result that excludes it conservative.

Should you have questions or would like to discuss this matter, please contact me (tmehan@awwa.org) or Kevin Morley (kmorley@awwa.org).

Sincerely,

G. Tracy Mehan, III
Executive Director – Government Affairs

cc: Peter Grevatt – EPA/OW/OGWDW
Eric Burneson – EPA/OW/OGWDW/SRMD
Russ Perkinson – EPA/OW/OGWDW/SRMD
Betsy Southerland – EPA/OW/OST
Betsy Behl – EPA/OW/OST/HECD

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Comments on "Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses"

November 23, 2016

Prepared for the American Water Works Association

By

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Synopsis

The physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model of EPA (2016a) accounts for exposure differences and biological differences across life stages, including sensitive life stages, and is a good start at understanding the complexities of iodine nutrition, perchlorate exposures, and sensitive populations. However, EPA (2016a) will need to carefully explain the designation of thyroid or pituitary hormone changes as critical effects, in contrast to NAS (2005) and EPA's own definitions (EPA, 2016b). EPA will also need to support their assumption of 2.5th to 10th percentile of fT4 as a hypothyroxinemia range, and incorporate symporter up regulation in the model.

Specifically, EPA could select as a point of departure the perchlorate dose associated with a lower 2.5th percentile of fT4 in the chosen sensitive population. If so, EPA will need to support the assumption that this lower 2.5th percentile evokes changes in TSH, which, although not technically the critical effect, may be a reasonable surrogate for thyroid hyperplasia and hypertrophy, which is/are the known precursor to the first adverse effect from perchlorate exposure (NAS, 2005, page 111). Alternatively, EPA could revise the model so that changes in TSH could be explored as the basis for its point of departure (POD). Such TSH changes are closer to the critical effect of perchlorate.

In addition, if EPA selects an iodine-deficient subpopulation as one of the sensitive populations as the basis for its RfD or MCLG, then EPA should acknowledge that this choice is conservative, and further, reduce or forgo an uncertainty factor for within human variability in the development of the RfD or MCLG.

We also highly recommend that EPA carefully consider any deviations between the model output and observations from prospective epidemiology studies, and specifically encourage EPA to carefully review the work of Crump et al. (2000) and Tellez et al. (2005) for applicability to the US. This review would be consistent with one of the conclusions of the NRC (2005, page 69).

Furthermore, we highly recommend that EPA consider how the modeled perchlorate dose response assessment might be modified by up regulation of symporter expression in the perchlorate dose range of interest. If up regulation is occurring, then it needs to be addressed in the model, or if this is not possible, then EPA should acknowledge that the unmodeled up regulation leads to a more conservative RfD or MCLG, all other factors remaining the same.

Finally, and as EPA already knows, from a clinical perspective lactation is associated with iodine uptake in the breast, and, there is a well-documented clinical increase in thyroid hormone requirements during pregnancy. However, colleagues of the University of Cincinnati, College of Medicine are unaware of any clinically increased rate of hypothyroidism in breast-feeding women compared to those choosing to feed their children formula. Thus, pregnancy and its increased thyroid hormone requirements have a far greater impact on the mother than breast-feeding.

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We encourage EPA to further explore the clinical relevance of the breast-feeding maternal population prior to choosing it for any point of departure in developing an RfD or MCLG.

Specific Comments

In the Science Advisory Board (SAB) 2013 review of perchlorate, they concluded that EPA should:

1) **Consider exposure to the following sensitive life stages: the fetuses of hypothyroxinemic pregnant women and infants exposed to perchlorate through either water-based formula or the breast milk of lactating women.**

   Response:

   We agree that protecting these life stages will protect other, less sensitive subgroups in our population. Previous Reference Doses (RfDs) for perchlorate were either based on human adults (NRC, 2005; EPA, 2016c) or children (Strawson et al., 2004a,b,c), with an uncertainty factor for within human variability that varied due to the population chosen (10-fold for NAS & EPA and 3-fold for Strawson et al.). EPA's choice of either fetuses of hypothyroxinemic pregnant women and/or infants exposed to perchlorate through either water-based formula and/or the breast milk of lactating women further refines our understanding of the most sensitive population and can lead to a further reduction in the uncertainty factor for within human variability. EPA has reduced or obviated the need for this factor on a number of occasions when the sensitive human population was known (e.g., Dourson et al., 2001).

   However, while EPA's appropriate focus is on one or more of the sensitive populations above, its potential selection of a nutritionally deficient subgroup as the basis of a revised RfD, specifically, an iodine-deficient subpopulation of one of these sensitive populations may be a first. To our knowledge, EPA has never determined a RfD, Reference Concentration (RfC), or risk specific dose (RSD) on the basis of a nutritionally deficient experimental animal or human population. If EPA selects an iodine-deficient subpopulation of one of these sensitive populations as the basis for its RfD, then it should acknowledge that this choice is conservative, and further consider whether an uncertainty factor for within human variability is needed.

   In the case of perchlorate, US populations traditionally considered to be iodine deficient, such as vegetarians, may not be so, or if so and used as the basis of an RfD, then an uncertainty factor for within human variability may not be needed. For example, Fields et al. (2005) state:

   > Recent risk assessments of environmental perchlorate have been subject to much debate. A particular concern is whether appropriately susceptible sub-populations have been identified. Iodine-deficient

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> pregnant women, especially vegetarians, have been proposed as such a potential susceptible sub-population, but there is no evidence of iodine deficiency in the US population and the adequacy of iodine nutrition has not been studied in US vegetarians. To understand the possibility that US vegetarians might be iodine deficient, we reviewed the prevalence, demography, and lifestyle characteristics of US vegetarians as well as the world literature on iodine nutrition in vegetarians. Our findings indicate that strict vegetarians and vegans, who comprise probably less than 0.1% of the US population, have higher education, higher incomes, and healthier lifestyles than the general population. Field studies indicate that vegetarian diets need not lead to iodine deficiency and vegans may suffer excess iodine intake. It remains uncertain whether there are iodine-deficient vegans or pregnant women in the US. Of more general concern is whether the 10-fold default uncertainty factor is needed for intraspecies (i.e., within human) variability to protect such hypothetical susceptible sub-populations.

In dramatic contrast, iodine deficient populations may not be more sensitive to perchlorate exposures than populations that are iodine replete. This counter-intuitive proposition is supported, for example, by Steinmaus et al. (2016) who show that while the adjusted associations for their **total cohort** were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = –0.70; 95% CI: –1.06, –0.34] and decreasing free thyroxine (fT4) (β = –0.053; 95% CI: –0.092, –0.013), these associations were driven entirely by **the high iodine subcohort**. What these data show are that in low iodine situations, perchlorate is not having an effect on thyroid hormone production. A more appropriate conclusion from the Steinmaus et al. (2016) would be that perchlorate does not affect low iodine populations.

What might be happening biologically to support this observation?

One possible explanation may be the up regulation of symporter protein production in low iodine situations, leading thyroid cells to create additional symporter iodine channels. If this occurs in low iodine situations, then the thyroid gland would have more channels available for iodine intake, and perchlorate would have commensurately less effect in iodine uptake inhibition. Unfortunately, Steinmaus et al. (2016) did not measure symporter protein production in their cohort, but EPA's model can be revised to account for this by including a parameter for symporter protein up regulation, as described later in these comments.

Importantly, if EPA assumes that iodine deficiency is a sensitive condition and choses to use this in its modeling, then this choice should be associated with a commensurate reduction in the use of the uncertainty factor for within human variability. A 1-fold factor would be appropriate and consistent with other extant EPA choices of 1-fold for the within human variability uncertainty factor for

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RfDs with equivalent or even less data than what are available for perchlorate (e.g., benzoic acid, fluoride, and manganese) or RfCs (e.g., beryllium) on EPA's Integrated Risk Information System (EPA, 2016d).

2) **Derive the MCLG using a physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) model to account for exposure differences and biological differences across life stages, including sensitive life stages. Specifically, the SAB found that the 'default algebraic approach provides limited ability to address the various exposure and biological factors affecting sensitivity to perchlorate at different life stages. The SAB concluded that, from a scientific standpoint, it would be more appropriate to base the MCLG derivation on the perchlorate mode of action, using PBPK/PD modeling to relate perchlorate concentrations in drinking water to biological effects rather than the default approach.**

Response:

We agree that development of a PBPK/PD model to replace the usual No Observed Adverse Effect Level (NOAEL) and its associated default uncertainty factors is progressive. However, it will be important for EPA to carefully explore its underlying assumptions of critical effect (more about this in later comments), and check its modeling results with observations of thyroid hormone changes, or their absence, in human populations with different perchlorate exposures. For example, the prospective epidemiology study of Tellez et al. (2005) measured perchlorate in drinking water, breast milk and blood, and monitored iodine and thyroid hormone levels during pregnancy and post birth in mothers and their newborns. This study also monitored nitrate, selenium, iodine, lithium, and arsenic, which were known to be present in the environment of the three different populations studied by Tellez et al., and also which to some extent have been linked to thyroid dysfunction. This study also accounted for sources of perchlorate other than drinking water. Tellez et al. (2005) concluded that effects to the maternal or neonatal thyroid were not seen at water concentrations up to 114 ug/L. Specifically Tellez et al. (2005) state:

> We have conducted a longitudinal epidemiologic study among pregnant women from three cities in northern Chile: Taltal with 114 g/L, Chañaral with 6 g/L, and Antofagasta with 0.5 g/L perchlorate in the public drinking water. We tested the hypothesis that long-term exposure to perchlorate at these levels may cause a situation analogous to iodine deficiency, thus causing increases in thyrotropin (TSH) and thyroglobulin (Tg) levels and decreased levels of free thyroxine (FT4), in either the mother during the early stages of gestation or the neonate at birth, or in the fetus cause growth retardation. We found no increases in Tg or TSH and no decreases in FT4 among either the women during early pregnancy (16.1 4.1 weeks), late pregnancy (32.4 3.0 weeks), or the neonates at birth related to perchlorate in drinking water. Neonatal birth weight, length, and head circumference were not different among the three cities and were consistent with current U.S. norms. Therefore, perchlorate in drinking water at 114 g/L did not

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> cause changes in neonatal thyroid function or fetal growth retardation. Median urinary iodine among the entire cohort was 269 g/L, intermediate between that of pregnant women in the United States at National Health and Nutrition Examination Survey (NHANES) I and at NHANES III and consistent with current World Health Organization (WHO) recommendations. Median breast milk iodine was not decreased in the cities with detectable perchlorate. Analysis of maternal urinary perchlorate excretion indicates an additional dietary source of perchlorate.

EPA's modeling results were based in part on this prospective epidemiology study. But EPA should also use results from Tellez et al (2005) as a negative control, that is to validate its modeling outputs, recognizing that these outputs need to be consistent with Tellez et al.'s observations, and with other, similarly appropriate, prospective epidemiology studies. In fact, a precursor study to Tellez et al. (2005), that by Crump et al. (2002) was used as a basis of the RfD by Strawson et al. (2004a) and also commented on by NRC (2005, page 69):

> In addition to those calculations, the [NRC] committee compared serum concentrations of TSH and thyroid hormones reported by Crump et al. (2000) in children 6-8 years old with those children of similar ages in the United States during a comparable period (Zurakowski et al. 1999) as another approach to assessing whether data from the Chilean study might be useful for evaluating the U.S. experience. With the exception of serum T3, which is known to vary more depending on the assay method used, the mean serum thyroid hormone concentrations were not markedly different between U.S. and Chilean children. The mean TSH concentrations were somewhat higher in Chile but were not accompanied by decreases in serum T4 concentrations. Those results suggest that mean serum thyroid hormone concentrations in Chilean children were similar during the period to those in U.S. children of the same age. On the basis of the iodide-inhibition analyses, the additional comparisons, and a review of information on urinary iodide excretion, the committee concluded that the data from Chile could be considered in the evaluation of the U.S. experience with perchlorate in drinking water.

Collectively, these opinions show the value of the Chilean work and the usefulness of model calibration. The null hypothesis is that there is no relationship between perchlorate and measures of thyroid function. The alternative hypothesis is that there is. Since Tellez et al. (2005) saw no effect in hormone levels, these data do not allow the model to be evaluated for effects above their range of perchlorate exposures, where the null hypothesis might be rejected. However, Tellez et al. can be used to identify false positive predictions, that is, a positive model predication by EPA in the range of a negative observations by Tellez et al. would suggest a problem with EPA's model.

Therefore, we highly recommend that EPA carefully consider any deviations between their model output and observations from such prospective epidemiology studies, and specifically encourage EPA to carefully review the work of Tellez et al. (2005) for applicability to the US. This review would be consistent with NRC (2005) conclusion.

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Calibration of the EPA's model is expected to be challenging for three reasons:

- few quantitative criteria exist for markers in the range of hypothyroxinemia; thus, EPA will need to support it assumptions of 2.5th and 10th percentiles as defining this range;
- a large variability in iodine and perchlorate intake may be occurring in populations used in this calibration; and
- data are variable due to physiological and biochemical factors that are not addressed in the model; for example, the model does not address up regulation of symporter protein (more about this later).

One suggestion proposed by Lumen et al. (2013) would be to perform Monte Carlo analysis to address variability in model output. We encourage EPA to do this. Alternatively, or perhaps in addition, a positive control is also needed. EPA's model should be calibrated against observations where perchlorate has an effect on T4 (total or free) or TSH. In this regards, a wealth of experimental animal information exists that may be helpful in this modeling. The TERA Center at the University of Cincinnati, College of Medicine has all of this information on file, and it is freely available for anyone to view.

The following comments are focus on the charge questions for the perchlorate peer review panel and incorporate recommended changes to the charge questions in **red text** submitted by the American Water Works Association on October 21, 2016.

Charge question 1:

Please comment on the following aspects of the BBDR model structure and integration of the submodels for iodide/thyroid hormones and perchlorate for each of the life stages of focus (i.e., lactating mother, breast-fed infant, and bottle-fed infant):

A. **Does the developed model structure adequately and accurately describe the physiology and kinetics of iodine, thyroid hormones, and perchlorate during different life stages specified above? Please specifically note the strengths and weaknesses of the model structure for each life stage.**
B. **Are the physiological and kinetic parameters for iodine, thyroid hormones, and perchlorate for these life stages supported by the published sources for those parameters or data used to identify parameters via calibration? Please identify any critical data gaps or additional data on these model parameters.**
C. **Does the body up regulate the production of thyroid sodium-iodine symporters in the area of hypothyroxinemia prior to the stimulation of TSH? If so, how might this up regulation affect the modeling results?**

Response

One question that is not currently addressed by the model is the effect of increased sodium iodine symporter (NIS) expression on thyroid iodine transport in the presence of perchlorate-induced expression of the NIS gene, and more dramatically, the

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increase in production of the associated protein(s). For example, it is well documented that iodine deficiency, and possibly perchlorate exposure, facilitate baso-lateral localization of the iodine symporter, making it easier for the thyroid cell to acquire iodine. Further, simple Michaelis Menten kinetic modeling of transporter velocity, with the inclusion of terms for competitive perchlorate inhibition, suggests that modest increases in transporter expression (i.e. 2 to 5-fold expression) could provide compensation for perchlorate inhibition over a range of serum iodine concentrations. This may be an important factor since a perchlorate concentration of 150 ppm (~15 mg/kg-day) was reported to induce NIS mRNA in postnatal day 25 rat pups by about 1000%, and in dams by 5-fold (Taylor, 2008. At this high dose, NIS protein levels could be induced to even higher levels than indicated here since posttranslational stabilization of both the transcript and the receptor protein have been implicated as important regulators of symporter expression.

While an open question remains in the dose-response relationship between perchlorate concentration and NIS induction, and whether a threshold dose exists below which little or no change in NIS expression occurs, EPA's model should be able to adequately account for homeostatic responses at steady-state perchlorate levels. Such responses may include compensatory changes that reestablish normal T4/fT4 levels; compensatory changes are not typically considered adverse. Model predictions should not focus on acute or temporally immediate effects of perchlorate; rather steady-state changes at equilibrium reflective of environmental exposures. A prediction on immediate perchlorate effects could be misleading if homeostasis is rapidly reestablished by normal compensatory physiological changes.

Therefore, we highly recommend that EPA consider how its modeled perchlorate dose response assessment might be modified by up regulation of symporter expression in the perchlorate dose range of interest. At the very least, such up regulation, if occurring and not otherwise addressed, would lead to a more conservative RfD or MCLG, all other factors remaining the same.

Charge question 5:

Given the lack of a specific quantitative clinical definition of hypothyroxinemia for the specific life stages evaluated (pregnant mothers, infants and lactating mothers) and that reference intervals of thyroid hormones reported in the literature are influenced by many factors (life stage differences, analytical method used, laboratory utilized, ethnicity, iodide nutrition, population size etc.), EPA developed a normalization procedure to derive hypothyroxinemia reference ranges.

A. **Please comment on whether the development of this hypothyroxinemia reference ranges ~~-~~is consistent with EPA's definition of critical effect, that is the first adverse effect or its known precursor as dose rate increases. Might a different effect such as changes to TSH be a more appropriate critical effect? If the former is ~~on the~~ more appropriate, then is this particular hypothyroxinemia range derived for pregnant mothers, fetuses,**

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lactating mothers, breast-fed infants and bottle-fed infants appropriate.

Response:

If hypothyroxinemia is considered to be the critical effect, then the development of a normalized range for hypothyroxinemia among studies seems appropriate, and EPA is to be commended for developing an easy to understand tool to effect its modeling.

However, the choice of hypothyroxinemia is not consistent with EPA's definition of critical effect, that is, the first adverse effect or its known precursor [singular] that occurs at dose rate increases (EPA, 2016c). Nor has EPA chosen such changes as sole critical effects with other of its assessments where the thyroid gland is impacted, as shown on Table X. Furthermore, the EPA model is a review of 3rd trimester hormone changes, however, neurological changes are expected from 1st trimester, which evokes questions including, why is a decrease in fT4 considered adverse for 7 days postnatal if this time is not associated with 1st trimester exposures? What level of decrease is considered adverse? Is maternal hypothyroxinemia itself the critical effect, or is it a "springboard" to possible neuro-developmental effects?

The concept of critical effect is embedded in a continuum of effects potentially associated with any exposure to xenobiotics and reflects a sequence of effects of differing severity. From least to most severe this continuum includes, adaptive effects, compensatory effects, the critical effect, adverse effects, and frank effects.

As EPA colleagues know, this continuum starts at:

- Low dose with upstream indicators of change, or adaptive effects, where the organism's ability to withstand a challenge is enhanced. Doses associated with such effects are often referred to as No Observed Adverse Effect Levels (NOAELs). The concept of hormesis may also be relevant here.
- As dose increases, compensatory effects occur, which enable the organism to maintain overall function without further enhancement or significant cost. Doses associated with such effects are also often NOAELs. Some of these effects might be judged to be the critical effect.
- As dose further increases, the critical effect is reached. This is the first adverse effect, or its known precursor, that occurs to the most [relevant or] sensitive species as the dose rate of an agent increases. Note that the bracketed phrase "relevant or" is important since the most relevant specie is always preferred over the most sensitive specie (e.g., if data shows that the rat is more sensitive than the human, the human data are still preferred), but when such information is not available, data from the most sensitive specie are chosen. Also the term "precursor" in this definition is singular, meaning the immediate precursor, not just any prior effect. This restriction is important both because it ties the concept of critical effect into common medical practice and because the resulting dose response—such as an RfD—is more meaningful. Specifically, without the

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restriction any RfD can be estimated.[1] Doses associated with such effects are Lowest Observed Adverse Effect Levels (LOAELs). The highest NOAEL below this LOAEL is generally used in the dose response, and the focus is on determining this NOAEL in a sensitive population.

- As dose further increases, the critical effect is exceeded, and adverse effects are manifested as biochemical changes, functional impairments, or pathologic lesions. These progressively more severe effects impair the performance of the organism, and/or reduce its ability to respond to additional challenges. At some point these adverse effects become manifestly overt and irreversible, and frank effects or disease ensues.

For EPA's perchlorate modeling, this continuum of effects means that determination of the critical effect is of utmost importance in developing RfDs and other dose response assessment values. This is because all chemicals will elicit effects at some dose, and the effects of many of these chemicals are beneficial (e.g., any macro or micro nutrient at essential levels and drugs when administered at recommended doses). However, all chemicals also elicit adverse responses. It follows that expert judgment, involving many disciplines, is needed to determine the critical effect, that is, the first adverse effect or its known precursor.

NRC (2005, page 111) defined the first adverse effect for perchlorate exposure as hypothyroidism (see attached Figure Z). This determination should guide EPA in its choice of the critical effect. According to both the NRC determination and EPA's definition, the critical effect would be hypothyroidism or its immediate precursor, thyroid hypertrophy/hyperplasia.

Given data on both hypothyroidism and hyperplasia/hypertrophy, the risk assessment focus would likely fall to the precursor lesion, that is, either hyperplasia and/or hypertrophy. Unfortunately, it is often difficult to determine modest stages of thyroid hypertrophy or hyperplasia in humans since routine biopsies to monitor such modest endpoints are contraindicated. The next most logical endpoint to monitor would be changes in thyroid and pituitary hormones, with changes in TSH more closely associated with doses that cause hyperplasia and/or hypertrophy. Thus, changes in TSH, or concurrently, changes in T4 that are expected or assumed to lead to changes in TSH, may be an appropriate focus for EPA's selection of critical effect. This means specifically, a change in fT4 to a level of the lower 2.5th percentile of the population as described on EPA (2016d, page 17):

> …and that hypothyroxinemia occurs for fT4 levels between the 2.5th and 10th percentile for the entire population. When fT4 falls below the 2.5th percentile for the entire population in a life stage, it is assumed that TSH levels would be

[1] Many examples of appropriate use by different groups are found on International Toxicity Estimates for Risk (*ITER*) database available at http://toxnet.nlm.nih.gov. An example of where this was not done appropriately is the NAS perchlorate assessment (2005, page 111). For a commentary on this inappropriate choice, see also Strawson et al., (2005).

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sufficiently elevated to trigger hormonal feedback, invalidating the model predictions.

Therefore, to determine an RfD or MCLG, EPA could select as its point of departure the perchlorate dose associated with a lower 2.5th percentile of fT4 in the chosen sensitive population. If so, then EPA will also need to support its assumption that this lower 2.5th percentile evokes changes in TSH, which, although not technically the critical effect, is a good surrogate for thyroid hyperplasia and hypertrophy, which is/are the known precursor to the first adverse effect from perchlorate exposure (NAS, 2005, page 111). Alternatively, EPA could revise its model so that changes in TSH could be explored as the basis for its point of departure (POD). Again, changes in TSH are closer to the critical effect than are changes in fT4.

However, in either case, EPA should recognize that basing a drinking water standard on a non-critical effect (the first adverse effect or an immediate precursor) is unprecedented and has broad implications for the overall regulatory approach. Thus, EPA will need to carefully explain that while hypothyroidism is the expected first adverse effect from perchlorate exposure (as per NAS, 2005, page 111), and while hyperplasia/hypertrophy are the immediate precursor, that neither one of these effects is easily monitored in human populations and, thus, pituitary or thyroid hormone changes, recognized as non-adverse and non-critical effects, are being used as points of departure for perchlorate. Importantly, such a choice by EPA for perchlorate does NOT indicate an overall change in policy. But rather, is necessitated by the unique perchlorate database. Especially since all chemicals have some effect on the human body at low levels, many of which are not adverse, EPA's decision needs to be carefully explained. Otherwise this decision has the potential to divert limited resources to actions that seek to mitigate nonadverse, or otherwise *de minimis* public health risks.

B. Based on the perchlorate dose level at which each life stage is predicted to become hypothyroxinemic (for a given iodine ingestion rate), it appears that the lactating mother is much more sensitive than the breast-fed infant for PND 30-90. In part this occurs because breast feeding reduces the iodide available for the maternal thyroid. Is this prediction biologically realistic and clinically relevant, and if so, should the subsequent analysis also consider the lactating mother as a life-stage of concern for MCLG derivation?

Response: From a clinical perspective, lactation is associated with iodine uptake in the breast, which is why medical doctors avoid treating lactating mothers with radioactive iodine. Furthermore, there is a well-documented clinical increase in thyroid hormone requirements during pregnancy, which is addressed by increasing thyroid hormone supplementation for hypothyroid patients, but typically with return to pre-pregnancy dosage postpartum. However, colleagues of the University of Cincinnati, College of Medicine are unaware of any clinically increased rate of hypothyroidism in breast-feeding women compared to those choosing to feed their children formula. Thus, pregnancy and its increased thyroid hormone requirements have a far greater impact on the mother than breast-feeding.

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We encourage EPA to further explore whether this lack of hypothyroidism in the maternal population who choses to breast-feed their infants is correct. If correct, then EPA's model that projects hypothyroidism in breast-feeding women is not correct.

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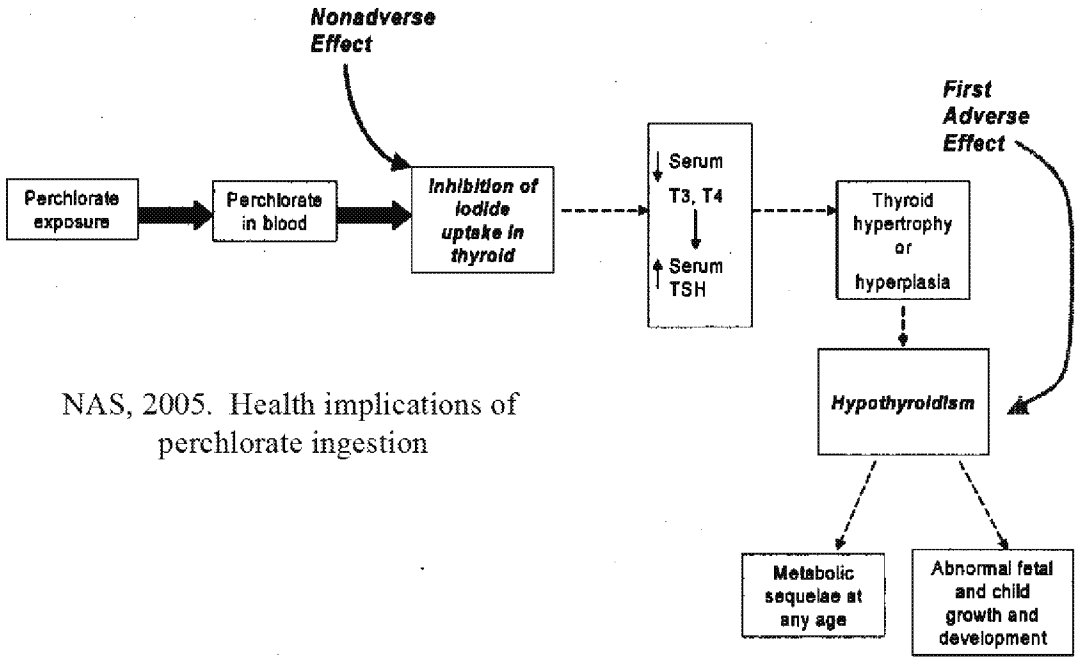

NAS, 2005. Health implications of perchlorate ingestion

FIGURE 5-2 Committee's suggested mode-of-action model for perchlorate toxicity in humans indicating first adverse effect in the continuum.

Figure Z. NRC (2005, page 111) description of effects with increasing perchlorate exposure, including the determination of the first adverse effect.

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Table X. Chemicals on EPA's Integrated Risk Information System (IRIS) with Thyroid Changes as one of the Critical Effects

Chemical Name	CASRN	Route	Assess. Type	Critical Effect or Tumor Type (selected)
Acrylamide	79-06-1	Oral	Cancer	Thyroid tumors and tunica vaginalis mesotheliomas
Apollo	74115-24-5	Oral	Noncancer	Four groups of 6 male and 6 female dogs were given diets containing varying doses of Apollo for 1 year. At dietary levels of 1000 and 20,000 ppm, the effects on organ weights included hepatocyte enlargement with eosinophilic cytoplasm; increased liver, thyroid, and adrenal weights; and elevated serum cholesterol, triglycerides, and alkaline phosphatase. Further studies in a 2-year feeding oncogenic rat study revealed that Apollo increased bile flow rate and shifted the pattern of thyroxine excretion to the feces, suggesting that Apollo may enhance clearance of thyroid hormones. The proposed mechanisms postulated that Apollo increased bile flow, causing an increase in metabolism and excretion of thyroxine. The reduced circulating thyroxine stimulated the pituitary gland through the hypothalamus to produce increased TSH. The elevated TSH stimulated the follicular cells and resulted in increased thyroxine and decreased colloid, follicular cell hyperplasia, hypertrophy and neoplasia in the male rat at the termination of the chronic study.
Benzyl chloride	100-44-7	Oral	Cancer	Thyroid, C-cell adenoma/ carcinoma
Bromate	15541-45-4	Oral	Cancer	Testicular mesothelioma, renal tubular adenoma and carcinoma, and thyroid follicular cell adenoma and carcinoma
Chlorine cyanide	506-77-4	Oral	Noncancer	Decreased weight gain, significant decreases in thyroxin levels and thyroxine secretion rates, and myelin degeneration in rats at 30 mg/kg/day cyanide (70 mg/kg/day chlorine cyanide); NOAEL: 10.8 mg/kg/day cyanide converted to 25.3 mg/kg/day of chlorine cyanide Proliferation of glomerular cells of the kidney and follicular cells that were low in height and

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Chemical Name	CASRN	Route	Assess. Type	Critical Effect or Tumor Type (selected)
				accumulation of colloid in the thyroid glands in young sows at about 9.45 mg/kg/day CN
Cumene	98-82-8	Inhale	Noncancer	Increased kidney weights in female rats and adrenal weights in male and female rats
Cyanogen bromide	506-68-3	Oral	Noncancer	Decreased weight gain, significant decreases in thyroxin levels and thyroxine secretion rates, and myelin degeneration in rats at 30 mg/kg/day cyanide (122 mg/kg/day cyanogen); NOAEL: 10.8 mg/kg/day cyanide converted to 44 mg/kg/day of cyanogen
Dacthal	1861-32-1	Oral	Noncancer	Effects on the lungs, liver, kidney, thyroid and thyroid hormones in males and females and eyes of females occurred (increased organ weight as well as an increase in the incidence and severity of follicular cell hypertrophy, hyperplasia and basophilic clumped colloid). Additionally, a dose-related decrease in thyroxine (T4) occurred throughout the study, and triiodothyronine (T3) was decreased in a dose-related manner at 52 weeks. Thyroid stimulating hormone (TSH) values were elevated at 52 weeks (dose related) and at 104 weeks (no dose response).
1,2-Dibromo-ethane	106-93-4	Oral	Cancer	Forestomach tumors, hemangiosarcomas, thyroid follicular cell adenomas or carcinomas
Dodine (ARCHIVED)	10/3/2439	Oral	Noncancer	Thyroid toxicity including changes in the shape of follicular epithelial cells of the thyroid from squamous to cuboidal and low columnar in 4/4 dogs; increased vascularity; and partially filled follicles that stained less intensely
Ethylene thiourea	96-45-7	Oral	Noncancer	Increased incidence of thyroid hyperplasia
Hydrogen Cyanide and Cyanide Salts	Various	Inhale	Noncancer	In workers (n=36) exposed to HCN for 5 – 15 years in three electroplating factories, statistically significant altered rates of iodide uptake by the thyroid, thyroid enlargement, and CNS symptoms were reported. Twenty of the exposed workers (26%) were identified with mild to moderate thyroid

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Chemical Name	CASRN	Route	Assess. Type	Critical Effect or Tumor Type (selected)
				enlargement. Radioactive iodine uptake measured following a 2-day break in HCN exposure indicated statistically significantly elevated iodide uptake after 4 hours (38.7 compared to 22.4%) and 24 hours (49.3 compared to 39.9%) as compared to controls In a study of silver-reclamation workers (n=36) examined an average of 11 months following exposure, serum thyroid stimulating hormone (TSH) levels in workers were significantly elevated relative to laboratory controls. T3 uptake in the highest exposed workers (n=9) was statistically significantly elevated compared to laboratory controls In an occupational study of electroplating workers exposed to HCN, workers (n=35) exposed for 5 years had significantly decreased T3 (48%) and T4 (37%) and significantly increased TSH (142%) as compared to controls. A significant negative correlation between T4 and SCN- concentrations were observed among 6 or 10 pigs per group (sex not specified and number of animals unclear due to inconsistencies in reporting) that were treated with KCN administered in the diet for 10 weeks, an in increase of 24% in thyroid weight was seen at 4.3 mg/kg-day. Histologic alterations were reported in the thyroid, liver, kidney, and CNS in all dosed animals. However, no incidence data or statistical analyses were provided for these histologic findings, precluding a characterization of the dose response for these effects. In a 24-week evaluation of the effects of gavage administration of KCN on behavior and thyroid function in miniature pigs, both triiodothyronine (T3) and thyroxine (T4) demonstrated a dose-related decrease (23 and 13%, respectively) that was statistically significant by week 18 of the study. In a 14-week evaluation of the toxicity of diet supplemented with NaCN corresponding to 0 or 1.04 mg/kg-day CN- in 22-week-old mongrel dogs (six males per group), an evaluation of the thyroid of

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Chemical Name	CASRN	Route	Assess. Type	Critical Effect or Tumor Type (selected)
				animals in this study showed that serum T3 was significantly decreased (55%) and thyroid weight was significantly increased (23%) in the cyanide exposed group.
Maneb	12427-38-2	Oral	Noncancer	Increased thyroid weight
4,4'-Methylene bis(N,N'-dimethyl)aniline	101-61-1	Oral	Cancer	Thyroid tumors, follicular cell carcinoma/ adenoma
Mirex	2385-85-5	Oral	Noncancer	Liver cytomegaly, fatty metamorphosis, angiectasis; thyroid cystic follicles
Nitrobenzene	98-95-3	Inhale	Cancer	Liver hepatocellular adenomas or carcinomas, kidney tubular adenomas or carcinomas, thyroid follicular cell adenomas or carcinomas
Norflurazon (ARCHIVED)	27314-13-2	Oral	Noncancer	Four groups of 4 male and 4 female beagle dogs were exposed to varying doses of Norflurazon in the diet for 6 months. At 450 ppm, effects were seen in the liver and the thyroid. Thyroid changes involved a slight increase in colloidal vacuoles.
Oryzalin	19044-88-3	Oral	Noncancer	Increases in serum cholesterol, alkaline phosphatase, and relative liver and kidney weights, and decreases in alanine transaminase and adrenal weights
Pentachlorophenol	87-86-5	Oral	Cancer	Hepatocellular adenomas or carcinomas and adrenal benign or malignant pheochromocytomas
Perchlorate (ClO4)	**7790-98-9**	**Oral**	**Noncancer**	**Radioactive iodide uptake inhibition (RAIU) in the thyroid**
Silver cyanide	506-64-9	Oral	Noncancer	Decreased weight gain, significant decreases in thyroxin levels and thyroxine secretion rates, and myelin degeneration in rats at 30 mg/kg/day cyanide (155 mg/kg/day silver cyanide); NOAEL: 10.8 mg/kg/day cyanide converted to 55.7 mg/kg/day of silver cyanide Proliferation of glomerular cells of the kidney and

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Chemical Name	CASRN	Route	Assess. Type	Critical Effect or Tumor Type (selected)
				follicular cells that were low in height and accumulation of colloid in the thyroid glands in young sows at about 9.45 mg/kg/day CN
Terbacil	5902-51-2	Oral	Noncancer	Increase in thyroid/body weight ratio; slight increase in liver weights; elevated alkaline phosphatase
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6	Oral	Noncancer	Decreased sperm count and motility in men exposed to TCDD as boys / Increased TSH in neonates
Thiophanate-methyl	23564-05-8	Oral	Noncancer	Decreased body weight, decreased spermatogenesis, and histological evidence of hyperthyroidism
1,1,2-Trichloropropane	598-77-6	Oral	Noncancer	Mild lesions in liver, kidney and thyroid; follicular collapse, reduction in colloid density and increased epithelial cell height in the thyroid
Trifluralin	1582-09-8	Oral	Cancer	Combined renal pelvis carcinomas, urinary bladder papillomas and/or thyroid adenomas and carcinomas
Zinc cyanide	557-21-1	Oral	Noncancer	Decreased weight gain, significant decreases in thyroxin levels and thyroxine secretion rates, and myelin degeneration in rats at 30 mg/kg/day cyanide (67.5 mg/kg/day zinc cyanide). NOAEL: 10.8 mg/kg/day cyanide converted to 24.3 mg/kg/day of zinc cyanide Proliferation of glomerular cells of the kidney and follicular cells that were low in height and accumulation of colloid in the thyroid glands in young sows at about 9.45 mg/kg/day CN
Zineb	12122-67-7	Oral	Noncancer	Thyroid hyperplasia

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Public Comments

Submitted By

Intertox, Inc

INTERTOX

COMMENTS ON US EPA'S

DRAFT BIOLOGICALLY BASED DOSE-RESPONSE MODEL (BBDR)

AND

DRAFT BIOLOGICALLY BASED DOSE-RESPONSE MODELS FOR THE EFFECT OF PERCHLORATE ON THYROID HORMONES IN THE INFANT, BREAST FEEDING MOTHER, PREGNANT MOTHER, AND FETUS: MODEL DEVELOPMENT, REVISION, AND PRELIMINARY DOSE-RESPONSE ANALYSES

Prepared for:

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November 25, 2016

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SUMMARY OF INTERTOX COMMENTS

On September 30, 2016, US EPA published a notice announcing the release of materials for public comment in the Federal Register (81 FR 67350). The materials will undergo peer review in support of US EPA's Safe Drinking Water Act determination to regulate perchlorate. The Agency requests comments on both the draft Biologically Based Dose-Response (BBDR) Model and an accompanying draft model report titled "Biologically Based Dose-Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses" (the "Report"). Prior to this submission, Intertox commented on the charge questions and the list of peer review candidates to US EPA's managing contractor, Versar, Inc. (Provided as Appendices A and B in our full report).

In this document we focus our scientific comments on the BBDR model and the US EPA Draft Report. This will be the first time US EPA has used a BBDR Model to inform development of a Maximum Contaminant Level Goal (MCLG).

Support for US EPA's Process

The use of the best available science—key to any scientific endeavor—is imperative as the basis to impose regulatory limits for any chemical.

- We agree that a science-based BBDR or physiologically-based pharmacokinetic/ pharmacodynamic model (PBPK/PD) model for the assessment of relevant physiological parameters can inform US EPA on the possible health impact of perchlorate exposure. This process, when done transparently and systematically, is scientifically defensible and Intertox supports such a process.
- The Agency has bifurcated, we believe appropriately, the scientific work into two parts with separate peer reviews. The first and current peer review is focused on the BBDR model and the second will focus on how to use the model to define an adverse effect level. These require different expertise to evaluate the issues and these peer reviews will produce stronger scientific assessments when they can be more focused.
- The Agency has sought the assistance of a peer review of the BBDR model and associated documents. US EPA has also provided opportunity for public and stakeholder comments; we intend these to be helpful to US EPA and the peer reviewers. We hope there will be the opportunity for public comments at the peer review meeting.

Improvements to US EPA Draft Model Report

US EPA's Report can be improved using a more systematic approach, increasing transparency, and providing additional information. Since not all of the peer reviewers will have modeling experience, they will rely on US EPA's report as the only information on the model and will not conduct an independent assessment. The summary of our review of the Report is:

- The document can be improved with a more systematic approach and greater transparency. For example, the literature review, as US EPA explains it, was discontinued in 2013, yet the Report uses several references published after 2013 leaving it unclear why these were included while others were excluded. Additionally, when references for parameters are cited, the reference may be for another model, not the original study, leaving the reader unclear as to what literature is available for the parameter and why this value was chosen over others in the distribution for use in the model.

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- The Agency's cited literature will benefit by a complete literature review to support its conclusions. The portion of the data that the document relies upon is limited and would raise issues for US EPA on fundamental scientific rigor.
- The figures presented in the Report make it difficult to interpret the relevant data, that is, daily doses below 1 μg/kg-d. US EPA should consider tables of data (rather than figures) and focus the figures on the relevant environmental dose range for perchlorate (0-1 μg/kg-d).

Improvements to US EPA's BBDR Models

The model can be improved providing additional support in integrating the model code, increasing transparency in the output, and improving the ability of the model to predict both perchlorate and iodine deficiency with no perchlorate. For US EPA's two models, the model code was released in both acslX (Aegis Technologies, Inc.) and "R" languages (BBDR Models). The summary of our review of the model is:

- The model's only output being considered is the effect on free thyroxine (fT4) and no other measures of thyroid function. To understand the complex feedback and homeostatic mechanisms in the hypothalamic-pituitary-thyroid axis, several measures of thyroid function should be modeled (e.g., TSH, thyroglobulin, and thyrotropin releasing hormone).
- The Agency must increase transparency and resolve the inconsistencies in the BBDR model code. For example, it is nearly impossible for a peer reviewer to implement a working model by reading the documentation provided by US EPA. The fact that codes for two different platforms were available allowed us to query one code set to understand a second the code.
- The models are extremely difficult to set up and run and we have great concern that the compressed time frame for peer review will limit the ability of the peer reviewers to critically review the model. This includes the instructions, definition of parameters, and download of all software necessary to use the model.

Overarching Concerns

The Agency would improve the process and increase scientific rigor greatly by addressing the following:

- The endpoint of hypothyroxinemia, despite the US EPA's recent SAB review, is not a scientifically robust endpoint for evaluation of an adverse effect. Other thyroidal parameters (e.g., TSH and fT4) will be more consistent with adverse thyroidal effects and clinical values in the literature.
- The Model does not include other goitrogens with the same mechanism of action as perchlorate. These should be included in the BBDR model analysis. There are accepted methods to account for potency and mass that would increase the applicability to the Model.
- A fundamental concept in modeling the key mechanism of action of perchlorate (and other goitrogens) is to predict iodine deficiency without the influence of any other agents. Modeling iodine deficiency accurately would be the necessary first step in ensuring the credibility of the BBDR models.
- The Model predicts changes in thyroid hormone well below the known threshold for effects. As noted in the figure below, we have concerns about the model because it is inconsistent with the decades of scientific literature in animals and humans as well as the uncontested

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mechanism of action. For example, the model predicts changes in fT4 in the lactating woman with any addition of perchlorate. NRC (2005) estimated that approximately 75% inhibition of iodide uptake daily (a non-adverse precursor to thyroid hormone changes) would be necessary to cause any adverse effect. US EPA's model predicts that 75% iodide uptake would require a dose of over 500 µg/kg-d in a lactating woman (Figure B-7 in the Report). A dose of 500 µg/kg-d has not been reported to cause changes in thyroid hormone (Greer *et al.*, 2002; Braverman *et al.*, 2006). The model should be able to reliably predict such data.

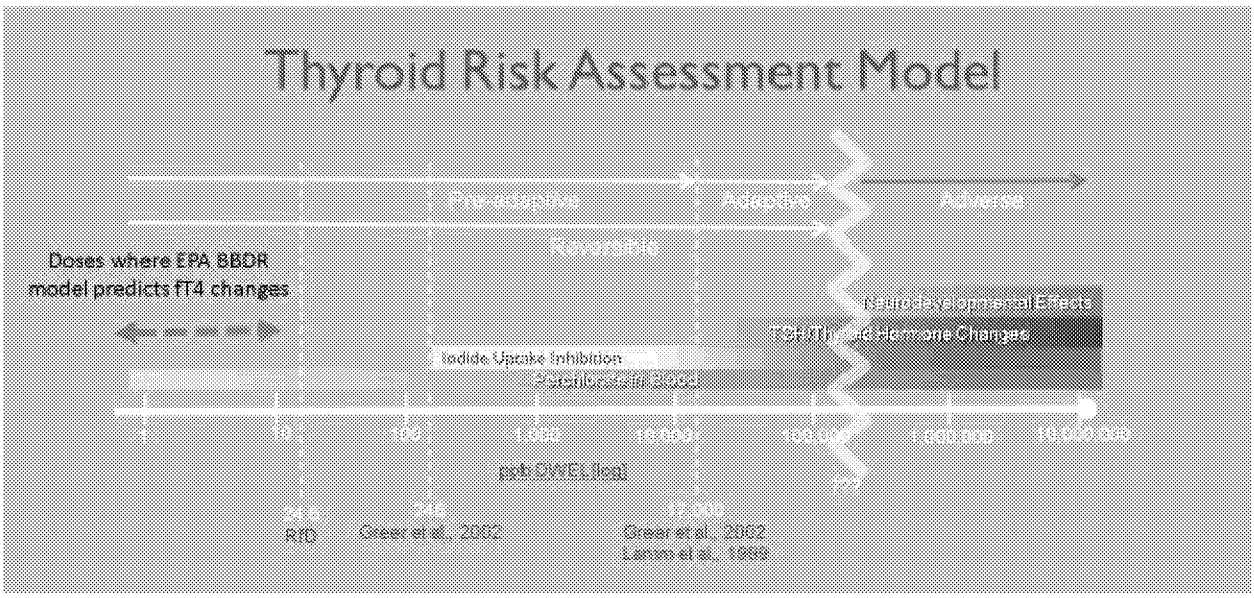

FIGURE A. REPRESENTATION OF THE DOSE-RESPONSE CURVE (IN WATER CONCENTRATION USING STANDARD US EPA CONVERSION FACTORS) FOR PERCHLORATE

See Figure 2 for more detail.

- It is difficult to fully review the model without knowing how US EPA will use it. It is scientifically useful to know how the data output from a BBDR model will be used as it allows for the understanding of the level of sensitivity required by the model.
- Extend the time for evaluation of the model. As noted in comments to Versar (Appendices A and B), we do not understand how US EPA expects a qualified scientist to download, troubleshoot, evaluate model code, evaluate model parameters, review US EPA's Report, and provide meaningful comments for this peer review given the short time for evaluation. We appreciate the additional 10 days, however, that still does not allow the thoughtful and scientific approach one needs to evaluate any BBDR model.

Overall, we agree with the approach and process US EPA is taking. We commend US EPA on using an improved method compared to the algebraic method for deriving a regulatory value. We are deeply concerned that the work done thus far in developing this model will be abandoned because US EPA has not been able to transparently deliver, describe, and predict hypothesized effects of a chemical exposure because it has not fully developed and tested a complex model. With the best available science in mind, we hope these comments will be useful to US EPA and to the peer reviewers in focusing their review.

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1.0 INTRODUCTION

On September 30, 2016, US EPA published a notice announcing the release of materials for public comment in the Federal Register (81 FR 67350). US EPA released its document titled "Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses" (the "Report") and the code (the "Model") for its Biologically Based Dose Response (BBDR) model in both acslX (Aegis Technologies, Inc.) and "R" languages. There were actually two models that were released: the pregnancy model (pregnant woman and fetus) and lactation model (lactating woman and infant). Prior to this submission, Intertox commented on the charge questions and the list of peer review candidates to US EPA's managing contractor, Versar, Inc. (Provided as Appendices A and B).

In this document, we focus our scientific comments on the BBDR models and the US EPA Report. US EPA has not yet released any information on how it will derive a Maximum Contaminant Level Goal (MCLG) using information from the models. In June 2016, US EPA stated:

> EPA is considering deriving a perchlorate MCLG by linking BBDR model output to alterations in thyroid hormone status that result in alterations in neurodevelopment. The draft approach for deriving a perchlorate MCLG outlines an assessment of the literature linking alterations in thyroid hormone status to alterations in neurodevelopment. Based on the results of this literature review, the report describes potential approaches to set the MCLG based on the availability of the current literature and the output of the BBDR model, predicting the effects of perchlorate on serum thyroid hormone concentrations in infants exposed via ingestion of formula mixed with contaminated drinking water or breast milk (see 81 FR 10617, March 1, 2016).

In the interest in providing as useful summary of information on the Report and Model, we will summarize what US EPA is doing to ensure use and application of the best available science (Section 2.0), suggest improvements for the Report (Section 3.0), suggest improvements for the Model (Section 4.0), and discuss overarching concerns with both the model and report (Section 5.0). We hope that this information will be useful for both US EPA and the Peer Review in the interest of promoting strong scientific support for the regulatory process.

2.0 SUPPORT FOR US EPA'S SCIENTIFIC PROCESS

US EPA made the decision to regulate perchlorate in drinking water under the Safe Drinking Water Act. The use of the best available science—key to any scientific endeavor—is imperative as the basis to impose regulatory limits for any chemical. Every scientist understands that we live in a world of chemicals, some harmful, some helpful, and some necessary to life; the key to regulation is using scientific knowledge to determine what are safe levels of exposure. Often, there is little information to support regulatory determination. Perchlorate is unique in that there are more than 60 years of scientific studies for this chemical.

We agree that a science-based BBDR or physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model for the assessment of relevant physiological parameters can inform US EPA on the possible health impact of perchlorate exposure. This process, when done transparently and systematically, is scientifically defensible and Intertox supports such a process.

We further agree with the Agency's decision to bifurcate the scientific assessment of its scientific work into two parts. The first, and current part regards the BBDR model review. The second part will

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be an evaluation of the methods for applying the BBDR models to possible adverse effects. These require different expertise to evaluate the issues at hand and these peer reviews will be stronger when they can be more focused.

Finally, we agree with US EPA's decision to seek peer review on its current BBDR model and associated documents. We are pleased that there is an opportunity for public and stakeholder comments. Finally, we trust that the peer review will be conducted in a manner that allows collaboration between peer reviewers, the public, and stakeholders at the upcoming peer review meetings.

3.0 IMPROVEMENTS TO THE US EPA DRAFT MODEL REPORT

The report can be improved using a more systematic approach, increasing transparency, and providing additional information. Since not all of the peer reviewers will have modeling experience, they will rely on US EPA's report as the only information on the model and will not conduct an independent assessment. Without improved clarity on the sources and documentation of the parameters, a better understanding of what effects key components have on the modeling results, and better presentation of data, it may be possible to dismiss the analysis, particularly when the conclusions are not well supported.

The Model Report includes a main document that describes the model development and parameterization, calibration, a preliminary dose response assessment, and a sensitivity analysis. The appendices include parameter definitions, changes that the Agency made to the model, an analysis of differences among the various life stages, perchlorate clearance analysis, and an assessment of population fT4 levels (definition of hypothyroxinemia). The BBDR Model code and supporting document was initially released with a 45-day comment period that was subsequently extended by 10 days.

3.1 Aligning the Report to standard scientific report fundamentals

US EPA describes the literature review that was conducted as part of this process. Based on the description on p. 22 of the Report, US EPA only searched PubMed and this search was conducted in December of 2013. As the release date of the Report was September 2016, it is unclear why US EPA failed to update its search. Three years may have produced relevant data to strengthen the model inputs and, at a minimum, it is simply the scientifically thorough process, particularly given the importance of the development of this model for the regulatory process. In addition, no summary of the literature review is included. The number of studies found is given, but what those studies report and justification for using or not using them is not included in the Report.

It is also clear that US EPA did use certain data from papers published after 2013. A review of the References shows seven papers (excluding one by the lead author of the Report which is listed as "in press") published in 2014-2016. Since these were not found as part of the systematic review of the literature, it is unclear why these were chosen and added to the exclusion of others.

In many cases where the literature for a parameter is cited (e.g., Table 4 of the Report), the citation is for another model (e.g., Fisher *et al.* (2016), Lumen *et al.* (2013)). This suggests that the value is given based on a cited report, but the cited studies are not primary literature sources of the actual data. If one is to evaluate US EPA's parameter, it would require independent evaluation of the cited model report (e.g., Lumen *et al.* (2013)) which would cite the paper documenting the study that the value is derived from. It is unlikely that a peer reviewer will conduct this type of evaluation given the limited time for review.

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Finally, the Report is not specific about wording it uses in its evaluation. For example, US EPA uses the word "adequate" or "within the range" as descriptors of its analysis. For example, "Overall, the model predictions were considered adequate" (p. 60 of the Report). These descriptors lack any specificity. US EPA should explain what threshold (e.g., within one standard deviation) is necessary for results or predictions to be "adequate" or "in the range" and what would constitute results that are inadequate. Left as undefined, it is misleading to the reader who may consider "adequate" to have to some intrinsic relative standard.

3.2 Transparency in the analyses of report content

When describing and documenting a BBDR model, there are certain standard evaluations that should be included, well-documented so they can be replicated, and summarized in a meaningful way. US EPA has not accomplished this in the Report. The Report has headings that describe calibration, local sensitivity analysis, and evaluation of model structure changes. However, the documentation of these activities, among others, is incomplete; it's unclear whether these were done to scientific community standards and what effect these had on the overall analysis. For example, US EPA presents the results of the sensitivity analysis. First, these were conducted for the formula-fed and breast-fed infants only. It is unclear why US EPA focused on these groups only. Second, US EPA chose a 1% change from default values, again without giving any justification for the decision. Third, US EPA displays both graphics and tables with the results of the sensitivity analysis, but does not describe or summarize the results other than to say

> …the influential parameters were time-dependent, iodine-dependent, and perchlorate-dependent. The influence of perchlorate on iodine was more significant in the breast-fed exposure because the low predicted iodide transferred in milk at the lower maternal exposure of 75 μg/d.

A reader unfamiliar with conducting a sensitivity analysis on a PBPK model would have no context for why this was being done, what the results are supposed to mean for the model and its results, and how to use this information to interpret US EPA's model output.

Similarly, US EPA presents an appendix on model structure changes; however, does not summarize what these changes were and what effect they have on the relevant output of the model: fT4 changes in pregnant women, fetuses, lactating women, and infants. In our review of three parameters (Km for binding of perchlorate to the NIS, Vmax for transfer of perchlorate in breast milk, and the permeability-area diffusion constant for iodine transfer to breast milk), US EPA's changes all make the model predict lower fT4 levels (Table 1). When multiple parameters are altered to increase the conservatism individually, the cumulative effect may be an overly conservative and unrealistic model. US EPA does not describe the cumulative effect of all of the changes to the overall model.

3.3 Presentation of results

One of our main concerns with the Report is the presentation of data. The only way the relevant output of the model (fT4) is presented is in figures. These figures are dose-response curves with fT4 plotted against perchlorate dose. Each curve represents a different iodine intake level (75 μg/d up to 250 μg/d). Presenting the data in this way creates several concerns: uncertainty is unclear, relevant doses are disregarded, and it's difficult to compare small variations in doses.

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TABLE 1. CHANGES IN FT4 BASED ON US EPA'S CHANGES TO SELECTED MODEL PARAMETERS

Parameter Assumption	Population	Assumption (A) value ["New" US EPA Value]	Assumption (B) value [Previous Value]	acslX A	acslX B	% Change
Km for Binding of Perchlorate to the NIS (KMNIS_P)	Pregnant Woman	6×10^4 ng/L (= 6.0e2 nmol/L)	1.6×10^5 ng/L (= 1.6e3 nmol/L)	10.1786	10.3600	-1.75%
Km for Binding of Perchlorate to the NIS (KM_TPNG)	Lactating Woman	6×10^4 ng/L (= 6.0e2 nmol/L)	1.6×10^5 ng/L (= 1.6e3 nmol/L)	11.1056 (7 day)	11.1057 (7 day)	-0.0009% (7 day)
				7.4284 (60 day)	7.4297 (60 day)	-0.0175% (60 day)
Vmax for Perchlorate Transfer to Breast Milk (VMAXC_MKP)	Lactating Woman	4.52e4 ng/h/kg$^{0.75}$	2.0e4 ng/h/kg$^{0.75}$	11.1056 (7 day)	11.1063 (7 day)	-0.0063% (7 day)
				7.4284 (60 day)	7.4282 (60 day)	0.0027% (60 day)
Permeability-area Diffusion Constant for Iodine Transfer to Breast Milk (PAMKC_I)	Lactating Woman	0.001 L/h/kg$^{0.75}$	0.002 L/h/kg$^{0.75}$	11.1056 (7 day)	11.1087 (7 day)	-0.0279% (7 day)
				7.4284 (60 day)	7.4713 (60 day)	-0.5742% (60 day)

US EPA has stated that there is uncertainty in the modeling results for 75 and 100 µg/d maternal intake of iodine. US EPA states

> Model predictions are also shown for 100 and 75 µg/d iodine, but the results for 100 µg/d are near the bottom of the provisional reference range, and are much more uncertain. At 75 µg/d the pregnant mother is predicted to be below the provisional 2.5th population percentile, hence in the hypothyroid range, even without perchlorate exposure (Figure 10, lowest curve, shown in grey). Those results are included, even though the entire 75 µg/d curve is currently considered uncertain, in the event that it is later determined that model predictions are valid for lower levels of fT4.

Although US EPA suggests that at some later time, the data may prove to have greater predictive power (it is unclear how this would occur), it is misleading to include it here currently. It appears to the reader that there are doses of perchlorate that drive fT4 far below US EPA's hypothyroxinemic range. EPA should not include data which are considered uncertain, such as the 75 µg/d iodine intake.

The Report figures present doses of perchlorate from 0 to 20 µg/kg-d (equivalent of 700 ppb in drinking water assuming a 70-kg adult drinking 2 L/d). US EPA states

> Comparing the predictions with the perchlorate sub-model to the radio-iodide uptake data of Greer *et al.* (2002) (for adults, the lactating mother, see Appendix B) indicated that the model is only accurate for prediction of iodide uptake inhibition up to an exposure level of ~ 100 µg/kg/d perchlorate. However, dose-response analyses were restricted to 0-20 µg/kg/d perchlorate, since that is the range of interest and likely application, and because predicted ft4 levels for many of the life-stages and iodine intake levels fell below their respective reference levels in this range.

Even doses up to 20 µg/kg-d are much greater than relevant for environmental exposures. The average dose of perchlorate from all sources in the US based on NHANES is 0.066 µg/kg-d and the

95th percentile is 0.234 µg/kg-d (Blount *et al.*, 2010). The RfD for perchlorate is 0.7 µg/kg-d (US EPA, 2005). If US EPA is intending to use this model to determine an MCLG for perchlorate, it is important to reliably evaluate doses in the relevant range both for exposure and for potential regulatory values. It is clear that doses greater than 1 µg/kg-d are irrelevant to this exercise (Figure 1).

This is a difficult point to understand given the figures as the only means to interpret the data. The line are bulky and difficult to discriminate between. In other figures where actual data from calibration studies are presented, the markers are incorrectly sized for readability or are a shape/design that has low quality. A table presenting the model data should also be included. The code to do so is not included in the model which requires an understanding of computer coding and model output to write code to accommodate this. For example, Intertox was able to do this to evaluate the data more precisely. In the pregnant woman (Figure 1), the corresponding table of data (Table 2) would clearly demonstrate no hypothyroxinemia with iodine intake of 150 µg/d and greater.

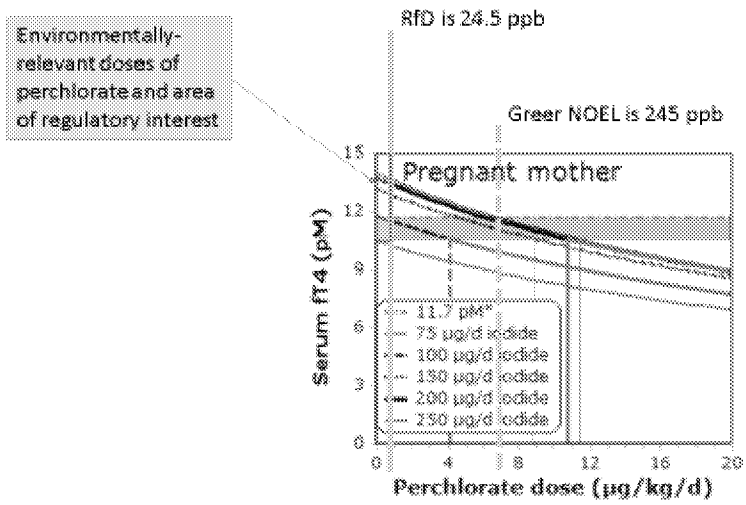

Figure 10. Free T4 (fT4) levels as a function of the perchlorate exposure and dietary iodine ingestion in the gestation ~week 40 pregnant mother and fetus. (Fetus graph not reproduced here as EPA does not report effects. See EPA document for graph.)

FIGURE 1. FIGURE 10 FROM US EPA'S MODEL REPORT REPRESENTING BBDR MODEL OUTPUT FOR PREGNANT MOTHER

Green lines are added to this reprint of the figure to demonstrate the approximate doses for two relevant endpoints. The first is US EPA's Reference Dose which is 0.7 µg/kg-d (24.5 ppb using US EPA standard conversion factors) and the dose for the NOEL in Greer *et al.*, 2002 which is 7 µg/kg-d (245 ppb using US EPA standard conversion factors). Note that the relevant perchlorate water concentrations in drinking water in the US are below 24.5 ppb. The US EPA BBDR model for the pregnant woman focuses on doses considerably higher.

TABLE 2. MATERNAL FT4 (PM) BASED ON IODINE INTAKE AND PERCHLORATE DOSE FROM EPA BBDR MODEL

Perchlorate Dose µg/kg-d	Iodine Intake 75 ug/d	100 ug/d	150 ug/d	200 ug/d	250 ug/d
0	10.46	11.77	13.17	13.74	13.98
0.1	10.43	11.74	13.13	13.70	13.93
0.2	10.40	11.71	13.09	13.66	13.89
0.3	10.37	11.67	13.05	13.62	13.85
0.4	10.35	11.64	13.02	13.58	13.81
0.5	10.32	11.61	12.98	13.54	13.77
0.6	10.29	11.57	12.94	13.50	13.73
0.7	10.26	11.54	12.90	13.46	13.69
0.8	10.23	11.51	12.87	13.42	13.65
0.9	10.21	11.48	12.83	13.38	13.61
1.0	10.18	11.45	12.80	13.35	13.57

4.0 IMPROVEMENTS TO THE US EPA DRAFT BBDR MODELS

This will be the first model used by US EPA to determine an MCLG. The Model is focused on the condition of hypothyroxinemia as an indicator of the potential adverse health effects. This draft model predicts the effects of perchlorate on serum thyroid hormone concentrations in the pregnant and lactating mother exposed to perchlorate in the diet and in infants exposed via ingestion of perchlorate in formula or breast milk.

The model can be improved providing additional support in integrating the model code, increased transparency in the output, and improving the ability of the model to predict both perchlorate and iodine deficiency with no perchlorate. Since not all of the peer reviewers will have modeling experience, they will rely on US EPA to provide the only information on the model and will not conduct an independent assessment.

4.1 BBDR model codes

The BBDR model was developed by integrating PBPK models for perchlorate and iodide with BBDR models for thyroid hormones to predict the effect of perchlorate on the thyroid gland in pregnant women and fetuses, formula-fed and breast-fed infants for the postnatal period from days 7 to 90, as well as lactating women. There were actually two models that were released: the pregnancy model (pregnant woman and fetus) and lactation model (lactating woman and infant).

4.1.1 Instructions are incomplete

We were pleased that US EPA released the code in two languages. We were aware that the manufacturer of acslX, Aegis Technologies, had decided to discontinue the software and no longer provide support as of December 2015. Recognizing this as an issue, as the BBDR model was developed in acslX, US EPA translated the code in to R, a free software platform for statistics. We are familiar with both platforms and have utilized both in this assessment.

The integration of both versions of the code is not straightforward. There are minimal instructions. The acslX code has no instructions included. The R code does have two very brief "README" files,

but requires significant time to download several files, software add-ons, and install the code. This will not be an easy process for the peer reviewers in the limited time.

4.1.2 Model variables and parameters are poorly documented

Once installed and operating, there are issues with the description and documentation of the model parameters. Model variables are poorly documented within the model. For example, M files in aclsX have no references for the basis of the variable. Proper and complete documentation is standard in PBPK modeling and utterly important given the uniqueness of this particular model

Each model (pregnancy and lactation) is broken into a number of subscripts and it is challenging to discern how the subscripts interact (e.g., in which order they are called, and where variable values change), especially when modifying/testing different variable values). Additionally, the code is not provided to produce full tabulated model output (e.g., thyroid hormone levels, serum perchlorate concentrations), and must be added to generate/evaluate this output (e.g., Table 2).

4.1.3 Models require separate input and transfer of data from one model to another

There are two separate models that were provided by US EPA: the pregnancy model (pregnant woman and fetus) and lactation model (lactating woman and infant). The lactation model starts with output from the pregnancy model, so to produce relevant output for the lactating mother/infant, the inputs (e.g., iodide and perchlorate intake) must be checked in each model separately to be sure they are consistent. This takes considerable time and attention and will be difficult for the peer reviewers to do under the limited time constraints.

4.2 Output of model

We note several issues of concern specifically on the model. The models are not dynamic models and are limited by steady-state assumptions, the model includes a lot of uncertainty, and the model cannot accurately model iodine deficiency (with no perchlorate exposure) which is a key component of the overall hypothesis.

4.2.1 Model considers steady state conditions

For a given model run, the model produces output based on iodide and perchlorate doses that remain constant throughout the model run (in units of μg/day for iodide and ng/kg-d for perchlorate). The model thus does not capture the expected variability in input of iodide and perchlorate with daily variations in diet, drinking water ingestion, and supplement intake. Further, for the pregnant woman, input parameters are held constant, corresponding to a single time point during pregnancy (at 40 weeks). The model does not account for the expected variability in biological/physiological parameters (e.g., body weight, body fat percentage, blood volume, daily urine volume) that occur as one advances through pregnancy. Conversely, for the lactating female, some parameters are assumed to change through time (e.g., body weight, percent body fat) while other parameters are held constant (e.g., daily urine volume).

The Report notes this limitation, stating:

> Because the only source of variability evaluated was iodide and perchlorate dietary intake, it is not expected that the model will capture the entire observed variability. Variability in physiological factors, such as urinary excretion rate and body weight, and biochemical factors, such as NIS expression and thyroid hormone synthesis activity, would also have significant effects on the metrics evaluated.

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Of note, US EPA could have considered the parameters probabilistically. For example, the model by Lumen *et al.* (2013) was adapted to include a wider functional range of iodine intake and to model populations using Monte Carlo (Lumen and George, 2016). An adaptation such as this would give greater insight into population variability and would provide a clearer impact of goitrogens.

4.2.2 Model lacks accuracy in predictions

The report section "Model Calibration Results" compares model outputs to literature values for similar populations. In general, the report states that model-predicted concentrations are "within reported values"; however, the report does not indicate that the model was adjusted based on these comparisons. Thus, it does not appear that these data were used to actually "calibrate" the model, i.e., to identify parameters to adjust to improve model accuracy and predictability. No other calibration based on model outputs is described.

The report compares model predictions to literature based values for only a limited number of parameters. The parameters compared to literature based values, and the source of those values, are:

- Urinary iodide for the formula-fed infant (Figure 4, top panel). Data compared are from Gordon *et al.* (2014) and Cao *et al.* (2010).
- Urinary perchlorate for formula-fed infant (Figure 4, bottom panel). Data compared are from Cao *et al.* (2010).
- Urinary iodide for the breast-fed infant (Figure 5). Data compared are from Gordon *et al.* (2014) and Cao *et al.* (2010).
- Urinary perchlorate for the breast-fed infant (Figure 6). Data compared are from Leung *et al.* (2012) and Cao *et al.* (2010).
- Breast milk iodide (Figure 7, top panel). Data compared are from Leung *et al.* (2012).
- Breast milk perchlorate (Figure 7, bottom panel). Data compared are from Leung *et al.* (2012).
- Serum T4 and fT4 for lactating mothers (Figure 8). Data compared are from NHANES.
- Serum T4 and fT4 for breast-fed infants (Figure 9). Data compared are from Cao *et al.* (2010), Leung *et al.* (2012), and Lem *et al.* (2012).

Examination of the cited studies confirms that while predicted model results do fall within the range of cited literature values, in each case, the range of values reported in the cited study is very broad suggesting that the model does not adequately capture all of the sources of variability that can impact these concentrations. Further, these comparisons suggest that predicted serum T4 and fT4 values are within "normal" ranges, even at relatively high perchlorate intake levels and for a range of iodine intake levels.

Cao *et al.* (2010) evaluated 92 full term infants between birth and 1 year of age each seen up to four times, as part of the Study of Estrogen Activity and Development (SEAD). Clinical visits took place at the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia. Perchlorate and iodide were measured in 206 urine samples, and fT4 was measured in 50 blood samples. Although the children consumed cow's milk formula, soy formula, or breast milk, no data on concentrations of perchlorate or iodide in formula or breast milk are provided and so comparisons of these data to model results for different assumed iodide intake levels (Figures 4, 5, and 9) are misleading. While Cao *et al.* (2010) do not present individual data values, Figures 4 and 5 plot individual urinary iodide concentrations reported in this study for formula- and breast-fed infants,

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respectively, for ages 0 to 90 days. Cao *et al.* (2010) also present their data in units of μg/g creatinine, not μg/L as in Figure 4. It is unclear how EPA obtained and transformed this data.

Since the figures present results on a log-scale, the true variability of values is not readily apparent. Indeed, urinary iodide concentrations measured in this population vary widely, from approximately 50-7,000 μg/L. For infants from 0 to 15 days of age, measured urinary iodide concentrations range from approximately 20 to 800 μg/L. By comparison, model-predicted urinary iodide concentrations for the breast-fed infant at day 7 range from about 58 to 201 μg/L for a perchlorate dose of 0.1 μg/kg-d and iodine doses ranging from 75 to 250 μg/day. Although model-predicted values are "within the range" of measured values as stated by US EPA, the range of measured values is extremely wide such that these comparisons provide little information about the predictability of the model. Further, these comparisons suggest that since the actual range of urinary iodide in a population is wider than predicted by the model, the model does not adequately capture all of the variability in population characteristics that can lead to widely varying urinary iodide concentrations. Given that Cao *et al.* (2010) did not provide formula or breast milk concentrations of iodine or perchlorate, it is impossible to use the Cao *et al.* data to assess the predictability of the model for specific iodine or perchlorate doses.

Similarly, Figures 4 and 6 plot individual urinary perchlorate concentrations measured in the Cao *et al.* (2010) study (although not presented in the paper) for formula- and breast-fed infants, respectively, for ages 0 to 90 days. Based on the figures, urinary perchlorate concentrations measured in these populations vary within a more narrow range than do iodide concentrations, from approximately 0.3-5.5 μg/L for formula fed infants and 0.05-12 μg/L for breast-fed infants. For infants from 0 to 15 days of age, measured urinary perchlorate concentrations range from approximately 0.3-5.2 μg/L for formula fed infants and from 0.08-4 μg/L for breast-fed infants. By comparison, model predicted urinary perchlorate concentrations for the breast-fed infant on day 7 at an iodine dose of 150 μg/day range much more widely, depending on the assumed perchlorate input: these estimates are approximately 0.09 μg/L for a perchlorate dose of 0.001 μg/kg-d, 0.9 μg/L for a perchlorate dose of 0.01 μg/kg-d, 9.8 μg/L for a perchlorate dose of 0.1 μg/kg-d, and 128 μg/L for a perchlorate dose of 1 μg/kg-d.

While Figure 9 shows that fT4 serum concentrations in breast-fed infants measured in Cao *et al.* (2010) ranged from about 5 to 22 pM, the geometric mean concentration of serum fT4 in breast-fed infants reported in the Cao *et al.* (2010) paper was much higher, or 42.5 pM (3.3 ng/dL) (95% UCL = 34.7-51.5 pM) (individual values are not reported). The reason for this discrepancy is not provided. By comparison, model predicted values were much different: for 7-day old breast-fed infants with a perchlorate dose of 0 μg/kg-d, predicted fT4 levels range from 20.5 to 26.4 pM for iodine intakes ranging from 75 to 250 μg/day, and for 7-day old breast-fed infants with a perchlorate dose of 1 μg/kg-d, predicted fT4 levels range from 19.9 to 25.6 pM for iodine intakes ranging from 75 to 250 μg/day. For 90-day old breast-fed infants with a perchlorate dose of 0 μg/kg-d, predicted fT4 levels range from 21.6 to 25.6 pM for iodine intakes ranging from 75 to 250 μg/day, and for 90-day old breast-fed infants with a perchlorate dose of 1 μg/kg-d, predicted fT4 levels range from 21.0 to 25.4 pM for iodine intakes ranging from 75 to 250 μg/day. The authors note that, for the 50 cases where both urinary perchlorate and serum thyroid hormone concentrations were available, "there was no significant association between TSH or T4 and perchlorate, thiocyanate and nitrate exposure."

Gordon *et al.* (2014) evaluated 95 breast-fed and/or formula-fed infants less than 3 months of age in the Boston area. Iodide concentrations were measured in single spot urine samples. Like the Cao *et al.* (2010) study, no data were reported on iodine concentrations in breast milk or formula, and urinary iodine concentrations measured widely: concentrations of urinary iodide for the full group

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ranged from 40-897.5 μg/L with a median of 197.5 μg/L. In breastfed infants (n = 39), the median urinary iodine concentration was 203.5 μg/L with a range from 61.5-395.5 μg/L, and in formula fed infants (n = 44), the median urinary iodine concentration was 182.5 μg/L with a range from 40-897.5 μg/L. Urinary iodine concentrations in infants who received mixed input from both breast milk and formula (n=10) were intermediate: the median was 197.8 μg/L, and the range was 123-592.5 μg/L). By comparison, model predicted values of urinary iodide for the breast-fed infant at day 30 range from about 65 to 184 μg/L for a perchlorate dose of 0.1 μg/kg-d and iodine doses ranging from 75 to 250 μg/day. The predicted urinary iodide concentration at the intermediate iodine dose of 150 μg/day was 129 μg/L. For this group, the model-predicted values tend to be substantially lower than the measured values; as above, the much wider range of measured values suggests that the model does not adequately capture the variability in population characteristics that can lead to widely varying urinary iodide concentrations. Again, while the model-predicted values are "within the range" of measured values; however, the range of measured values is extremely wide, indicating that the model does not adequately capture the variability in population characteristics that can lead to widely varying urinary iodide concentrations.

Leung *et al.* (2012) evaluated concentrations of iodide and perchlorate in breastmilk, maternal urine, and infant urine in 64 mother/infant pairs. The median iodide concentration was 45.6 μg/L (range 4.3-1,080 μg/L) in breastmilk, 101.9 μg/L (range 27-570 μg/L) in maternal urine, and 197.5 μg/L (range 40-785 μg/L) in infant urine. The median perchlorate concentration was 4.4 μg/L (range 0.5-29.5 μg/L) in breastmilk, 3.1 μg/L (range 0.2-22.4 μg/L) in maternal urine, and 4.7 μg/L (range 0.3-25.3 μg/L) in infant urine. By comparison, model predicted urinary iodide concentrations for the breast-fed infant at day 7 range from about 58 to 201 μg/L for a perchlorate dose of 0.1 μg/kg-d and iodine doses ranging from 75 to 250 μg/day. It is unknown what the source of perchlorate exposure and the daily perchlorate dose was in the population evaluated by Leung *et al.* (2012). By comparison, model-predicted urinary perchlorate concentrations for the breast-fed infant on day 7 at an iodine dose of 150 μg/day are approximately 0.09 μg/L for a perchlorate dose of 0.001 μg/kg-d, 0.9 μg/L for a perchlorate dose of 0.01 μg/kg-d, 9.8 μg/L for a perchlorate dose of 0.1 μg/kg-d, and 128 μg/L for a perchlorate dose of 1 μg/kg-d.

Again, EPA uses the imprecise phrase "within the range" to describe the model results compared to measured values reported by Leung *et al.* (2012). The range of measured values is very wide indicating that the model does not adequately capture the variability in population characteristics that can lead to widely varying urinary concentrations. Of interest, Leung *et al.* (2012) indicate that at these widely varying input levels, "There were no correlations between infant TSH or FT4 and iodine, perchlorate, and thiocyanate levels in breastmilk, maternal urine, and infant urine." Further, "In multivariable analyses, perchlorate and thiocyanate levels in breastmilk, maternal urine, and infant urine were not significant predictors of infant TSH or FT4." Finally, the authors note:

> Boston-area mothers and their breastfed infants are generally iodine-sufficient. Although environmental perchlorate and thiocyanate are ubiquitous, these results do not support the concern that maternal and infant environmental perchlorate and thiocyanate exposures affect infant thyroid function.

Thus, comparison of model outputs to these data, and the assertion that model outputs fall within the range of measured values, suggests that the model output is within normal population values.

Lem *et al.* (2012) measured fT4 and total T4 (TT4) in 512 children ages 0-18 years, to determine age-specific thyroid hormone reference ranges. The study does not report perchlorate or iodide intake levels or concentrations in any medium (e.g., urine or breast milk). Summary data are provided for

infants at 1 week, 1 month, and 3 months. As shown in Figure 9, model-predicted serum TT4 and fT4 concentrations in infants are within the reference ranges reported in Lem *et al.* (2012). However, the reference ranges are very wide—for TT4, the mean ranged from 132.6 nM at 1 week (2.5%ile = 75.9 nM, 97.5%ile = 239.1 nM) to 135 nM at 3 months (2.5%ile = 82.3 nM, 97.5%ile = 227.3 nM). For fT4, the mean ranged from 0.022 nM at 1 week (2.5%ile = 0.012 nM, 97.5%ile = 0.053 nM) to 0.020 nM at 3 months (2.5%ile = 0.013 nM, 97.5%ile = 0.037 nM). Lem *et al.* (2012) does not distinguish between breast-fed and formula fed infants. US EPA states, "Model-predicted concentrations of T4 and fT4 in both lactating mothers and breast-fed infants were within the range of literature reported values." However, given the wide reference ranges, this is not surprising. Model-predicted serum fT4 concentrations at a perchlorate intake of 0 μg/kg-d are highly dependent on assumed iodine intake levels (ranging from 0.020 nM at an iodine dose of 75 μg/d to 0.026 nM at 250 μg/d for the 7-day old infant and from 0.022 nM at 75 μg/d to 0.026 nM at 250 μg/d for the 90-day old infant). Further, even at a perchlorate dose up to 8 μg/kg-d, for iodide doses of 100 μg/d and above, predicted fT4 levels at 3 months exceed the mean reference value reported in Lem *et al.* (2012) for this age (0.020 nM).

The model sets the prediction of fT4 as a constant proportion of the TT4 concentration. Specifically, the model assumes that the fT4 concentration is 0.0001 times the TT4 concentration for the lactating mother, 0.00009 times the TT4 concentration for the pregnant mother, and 0.00017 times the TT4 concentration for the infant. These values are based on literature data. However, these fixed values do not capture the variability that can be associated with these estimates.

Some model parameters or compartments are modeled differently between the pregnant and lactating woman models, and an explanation of these differences or their impact on model predictions is not provided. For example, the pregnancy model assumes a value for the serum binding constant for perchlorate (VmaxC_Bp) of 585 ng/hr/kg (5.9 nmol/hr/kg$^{0.75}$), whereas the lactating model assumes a value of 1230 ng/hr/kg (12.4 nmol/hr/kg$^{0.75}$). In another example, the algorithm in the pregnant woman model for calculating plasma concentrations of iodide and perchlorate (RAplasma_i and RAplasma_p, respectively) includes an elimination term, whereas the lactating model does not.

4.2.3 Model cannot model iodine deficiency accurately

A fundamental concept in modeling the key mechanism of action of perchlorate (and other goitrogens) is to predict iodine deficiency without the influence of any other agents. Without the ability to model iodine deficiency, US EPA cannot propose that a particular agent can cause "iodine deficiency." Modeling iodine deficiency is necessary to ensure the utility of the BBDR models. US EPA did not develop a model that can be used to model iodine deficiency. Further complicating the model by adding in chemical exposure is akin to building on a weak foundation.

4.2.4 Lactating mother is more sensitive to iodine deficiency than pregnant

US EPA notes that the lactating mother is more sensitive to iodine deficiency:

> Some further analysis is needed to understand why, even with an iodine intake of 250 μg/d, the lactating mother is so much more sensitive to perchlorate than the formula fed infant.

Based on the output of the model and US EPA's defined hypothyroxinemia range, this is what is suggested. However, there are several important issues to consider. First, there are no studies that support greater effect of perchlorate on the lactating woman. Second, there are no studies to support an adverse effect of perchlorate on a lactating woman or her breast-fed child. Third, if we were to assume that the lactating woman does have decreased fT4 caused by a given perchlorate dose while her infant does not, the effect of low fT4 has different effects on an adult. Neurodevelopmental

outcomes are not a potential endpoint for exposure in a fully grown adult. Thus, if US EPA chooses to evaluate the lactating woman in a later assessment, they must define a different adverse effect that is relevant to her versus her infant.

4.2.5 Model results with doses lower than 1 μg/kg-d

If we do focus in on the results from the model that are below 1 μg/kg-d and results with fT4 levels greater than the 2.5th percentile (based on US EPA's hypothyroxinemic range), then for nearly all iodide levels in all life stages, the model does not predict hypothyroxinemia due to perchlorate exposure. The exception is the pregnant woman consuming 100 μg/d of iodine with perchlorate doses greater than 0.3 μg/kg-d.

In the lactating woman, US EPA notes that even without perchlorate, their model predicts hypothyroxinemia:

> Thus, the iodide levels and thyroidal stores for infants whose mothers ingest only 100 μg/d iodine are already compromised (though they may be sufficient for healthy development in the absence of perchlorate), hence these infants are more sensitive to any further decrease due to inhibition by perchlorate (Figure 13).

Taken together, US EPA's own data suggest that perchlorate exposure is not predictive of hypothyroxinemia (See Figure 1).

5.0 ISSUES OVERARCHING THE REPORT AND MODELS

There are several conceptual issues that are not specific to the Report or the Models, but are critical in consideration of the output and how the output will be used. Hypothyroxinemia is not an adverse effect, but since the current model cannot be used to evaluate changes in TSH, it is being considered the endpoint of concern. The model predictions are also inconsistent with animal data and the known MOA of perchlorate and other goitrogens.

5.1 Hypothyroxinemia as an endpoint

Diagnoses based on thyroid hormone measures are well-defined clinically. Overt hypothyroidism is considered an adverse effect and, if it occurs in a pregnant woman or infant, may affect the developing brain resulting in permanent impairment. Hypothyroidism is defined as sustained elevated TSH and low fT4. The NRC recognized hypothyroidism as the first adverse effect on the dose-response continuum (NRC, 2005). Subclinical hypothyroidism is elevated TSH with normal levels of fT4. Hypothyroxinemia is defined as low fT4 with normal levels of TSH.

US EPA has chosen to use hypothyroxinemia, not hypothyroidism, as the critical effect. The BBDR model can only predict levels of TT3 and TT4. Although fT4 is not mechanistically modeled, US EPA uses a fraction of TT4 to define fT4 levels.

5.1.1 US EPA's derived reference range for fT4

Although there is a reference range for TSH levels in different stages of pregnancy and in infancy, an analogous reference range does not exist for fT4. The reason is that different laboratories have variations in techniques and populations that make direct comparisons impossible. Therefore, in general, a laboratory will consider a cutoff for "low" or "high" based on the percentile in the batch it is testing. This cutoff is commonly the lowest 2.5th percentile, 5th percentile, or 10th percentile. There is no recommendation by any authoritative medical body on the appropriate cutoff.

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In its derivation of a provisional reference range, US EPA has arbitrarily chosen ranges with varying methods and confusing variation. For the pregnant women, US EPA describes a process for normalizing several studies in the literature although this methodology has not been verified or peer reviewed prior to the current review. For infants, values from Lem et al. (2012) were used. Possibly due to the variations in choosing these provisional ranges by life stage, there are discrepancies that are not explained. For example, it is difficult to understand why the 7-day old formula-fed infant has the 10th percentile fT4 at 16.9 pM while the 7-day old breast-fed infant 17.8 pM. The biological needs of a 7-day old infant should be independent of the feeding source.

5.1.2 Hypothyroxinemia is not an adverse effect

Transient hypothyroxinemia is not uncommon in pregnant women and severely premature infants (born at less than 28 weeks). In an individual, hypothyroxinemia is not considered adverse. The American Thyroid Association, American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics do not recommend treatment for hypothyroxinemia. The Endocrine Society suggests best judgement by the treating physician, however, does not recommend treatment in third trimester women (Furnica *et al.*, 2015).

Hypothyroxinemia as an endpoint to measure is questionable, particularly in pregnancy. There is a necessary rise in TT4, but also increased binding due to TBG, HCG, and other serum proteins. This results in hypothyroxinemia (low fT4), but no change in circulating T3 levels with T3 being the active hormone. It is hypothesized that hypothyroxinemia is an adaptive response by the body to maintain adequate hormone level (Furnica *et al.*, 2015).

US EPA may not use hypothyroxinemia as the adverse effect, per se. US EPA recently stated:

> EPA is considering deriving a perchlorate MCLG by linking BBDR model output to alterations in thyroid hormone status that result in alterations in neurodevelopment. (see 81 FR 10617, March 1, 2016)

There are studies that suggest an association between first trimester hypothyroxinemia and adverse neurodevelopmental outcomes in offspring. The literature on these outcomes is mixed. Most of the studies have small study populations and the inability to control for confounders over the study period (often years). Interventional studies have also reported that treatment of the mother with synthetic thyroxine normalizes thyroid hormone levels, but does not improve outcome compared to untreated (Lazarus *et al.*, 2011). Importantly, these studies all evaluate hypothyroxinemia in the first trimester with outcomes at two to three years of age. The BBDR model predicts hormone levels in the late stage (gestation week 40) pregnant woman.

Importantly, even if there were a high quality study that was able to demonstrate a causal relationship between first trimester hypothyroxinemia and adverse neurodevelopmental outcomes in offspring, the model is based on late-term (gestation week 40) pregnant women. The output from this model cannot be associated with this neurodevelopmental outcome.

5.2 The model does not account for compensatory mechanisms

The HPT axis of the human body is a dynamic system with both positive and negative feedback controls. This allows the body to tightly maintain availability of thyroid hormone levels to accommodate developmental needs or changes in diet or health. Both high and low levels of thyroid hormone can result in an adverse effect. The body is able to homeostatically regulate thyroid hormone, even in during periods of decreased iodine intake, by several different mechanisms. For example, decreased thyroid hormone would trigger TSH release from the pituitary gland which

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would increase NIS activity, stimulate iodination of thyroglobulin (Tg), stimulate organification of T4 and T3, increases turnover of Tg to make more thyroid hormone, and increase secretion of thyroid hormone to the circulation. The model by Lumen and George (2016) does empirically include homeostatic mechanisms.

The BBDR model does not include any compensatory mechanisms, such as TSH feedback or increase in NIS activity. US EPA has stated that

> …it is assumed that thyroid conditions occur for the fT4 levels between the 10th and 90th percentile of the entire population in a given life stage, and that hypothyroxinemia occurs for fT4 levels between the 2.5th and 10th percentile for the entire population. When fT4 falls below the 2.5th percentile for the entire population in a life stage, it is assume that TSH levels would be sufficiently elevated to trigger hormonal feedback, invalidating the model predictions.

Presumably, until the serum levels of fT4 fall below the 2.5th percentile, no change in TSH would be expected. Although there is no evidence to suggest this is correct, this suggests a more appropriate measure of adverse effect is below 2.5th percentile. However, even if US EPA changes its level to evaluate to 2.5%ile, this is still only a surrogate for change in TSH. And changes in TSH are not necessarily adverse unless sustained increased TSH is coupled with decreased fT4 (NRC, 2005).

Since the model does not include algorithms for calculating serum TSH levels, it cannot reliably predict thyroid hormone impacts for iodine intakes representative of iodine deficiency. When predicted fT4 levels fall below the "hypothyroxinemic range" in a functioning biological system, TSH would be expected to be elevated resulting in a feedback loop that would attenuate any effects. The model does not include this feedback loop. Thus, when model figures show predicted fT4 levels that fall below the hypothyroxinemic range, values are shown in grey to emphasize the uncertainty of these results.

5.3 Animal data on neurodevelopmental outcomes

There are several animal studies evaluating perchlorate exposure during pregnancy and neurodevelopmental outcomes (Bekkedal *et al.*, 2000; York *et al.*, 2001; York *et al.*, 2004; York *et al.*, 2005). The endpoints reported for each study are summarized in Table 3. These were controlled animal experiments with doses ranging from 0 (controls) to 30 mg/kg-d (30,000 µg/kg-d or 1,050,000 ppb), dosed orally during gestation. These studies all report no significant changes in the developmental endpoints measured.

5.4 Model predictions are inconsistent with the known MOA

The MOA of perchlorate is well understood and is not contested. Perchlorate affects the thyroid by competitively inhibiting iodide uptake to the thyroid through interaction with the sodium iodide symporter (NIS). This inhibition is reversible and not considered adverse. With sustained and significant inhibition—estimated to be about 70% inhibition for several months or more (NRC, 2005)—hypothyroidism could occur. Changes in thyroid hormone cannot occur without IUI; however, changes in thyroid hormones are not an inevitable consequence of IUI, that is, with cessation of exposure, no adverse health effects would occur.

The threshold at which radioactive iodide uptake (RAIU; the measure of IUI) occurs has also been determined in several clinical studies. A No Observable Effect Level (NOEL) for this nonadverse effect has been reported at 0.007 mg/kg-d (Greer *et al.*, 2002) and 0.04 mg/kg-d (assuming a 70 kg body weight; Braverman *et al.*, 2006; Lawrence *et al.*, 2001). The study by Greer *et al.* (2002) was

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TABLE 3. ANIMAL STUDIES ON NEURODEVELOPMENT AND ENDPOINTS REPORTED

Study	Doses	Endpoint	Result
Bekkedal *et al.*, 2000	0, 0.1, 1.0, 3.0, 10 mg/kg-d	General locomotor activity	No significant change in general locomotor activity due to prenatal and neonatal perchlorate exposure
York *et al.*, 2001	0, 0.3, 3.0, 30 mg/kg-d	F1 generation brain weights	No significant changes in developmental parameters were observed
York *et al.*, 2004	0, 0.1, 1.0, 3.0, 10 mg/kg-d	Juvenile brain weights, morphometry, and neuropathology (PND 12); Adult regional brain weights (PND 89), morphometry, and neuropathology; Passive avoidance and water maze testing, motor activity and auditory startle habituation	No effect on body weights, feed consumption, clinical observations, or sexual maturation of pups No behavioral effects as evaluated by passive avoidance, swimming water maze, motor activity, and auditory startle Significant decrease in follicular lumen diameter at ≥1 mg/kg-d (males)
York *et al.*, 2005	0, 0.1, 1.0, 3.0, 10 mg/kg-d	Motor activity (PNDs 14, 18, and 22) and juvenile brain weights, neurohistopathological examinations, and regional brain morphometry (PNDs 10 and 22)	Authors conclude that the NOAEL for maternal toxicity was greater than 10 mg/kg-d and the NOAEL for pup toxicity was 0.1 mg/kg-d based on the thyroid morphometric and histopathologic findings

the lowest reported NOEL for RAIU and the higher doses of 0.02, 0.1, and 0.5 mg/kg-d all resulted in changes in RAIU. This was supported by a separate clinical study reporting significant RAIU with exposure to 0.14 mg/kg-d (Lawrence *et al.*, 2000). None of these studies reported changes in thyroid hormones in any dose tested.

It has been suggested that these studies are in healthy adults and pregnant women or children may represent populations unusually sensitive to goitrogenic effects. However, there is nothing to support this hypothesis; rather, the NIS is highly conserved among species and the rate of uptake, affinity, and residence time of perchlorate or iodide is unlikely to vary for pregnant women or children.

The model predicts that perchlorate can change fT4 levels at doses lower than the threshold for IUI for pregnant and lactating women (See Figure 2). For example, the doses of perchlorate for the pregnant woman consuming 100 μg/d of iodide are listed in Table 2 (section 3.3 above). Based on this, there is a 2% decrease in fT4 levels occurring with an increase in perchlorate dose from 0 to 0.7 μg/kg-d. However, this is all 10-fold below the known NOEL for IUI of 7 μg/kg-d. This clearly is inconsistent with the clinical literature. In another example, the model predicts changes in fT4 in the lactating woman with any addition of perchlorate. NRC (2005) estimated that approximately 75% inhibition of iodide uptake daily (a non-adverse precursor to thyroid hormone changes) would be necessary to cause any adverse effect. US EPA's model predicts that 75% iodide uptake would require a dose of over 500 μg/kg-d in a lactating woman (Figure B-7 in the Report). A dose of 500 μg/kg-d has not been reported to cause changes in thyroid hormone (Greer *et al.*, 2002; Braverman *et al.*, 2006).

Second, the model's affinity constant is calibrated using the data from Greer *et al.* (2002). US EPA reports that the model accurately predicts no change from baseline in RAIU with exposures up to

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0.007 mg/kg-d. Thus, the model itself predicts changes in thyroid hormone without change in IUI. This cannot occur given the known MOA.

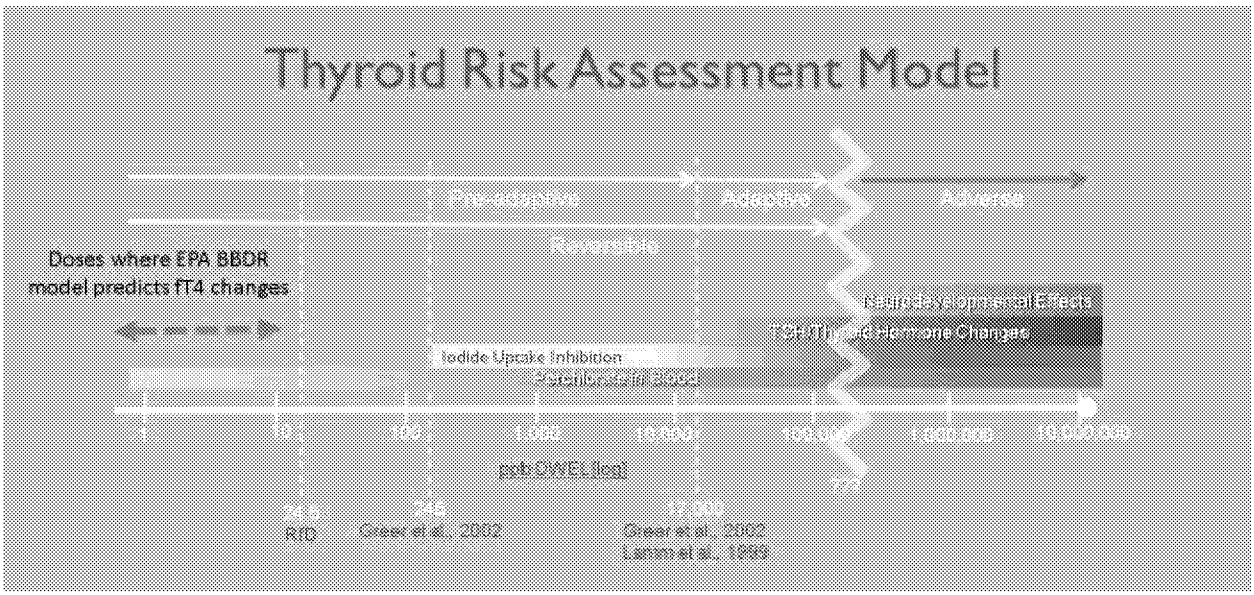

FIGURE 2. REPRESENTATION OF THE DOSE-RESPONSE CURVE (IN WATER CONCENTRATION USING STANDARD US EPA CONVERSION FACTORS) FOR PERCHLORATE

Summary of the dose-response of perchlorate on thyroid parameters and neurodevelopmental effects in offspring based on over 60 years of animal, clinical, and epidemiological data and reviews and consensus from multiple authoritative bodies. The three vertical white hashed lines represent the EPA Reference Dose (based on 0.7 µg/kg-d), the NOEL dose (7 µg/kg-d based on Greer *et al.* (2002)), and the high dose in Greer *et al.* (2002) where no change in thyroid hormone occurred (500 µg/kg-d). EPA's BBDR model predicts changes orders of magnitude lower than demonstrated in clinical studies and is contrary to the known mechanism of action (green arrow).

5.5 Daily background goitrogen load is not considered

Other chemicals have the same MOA as perchlorate and are found at levels in the diet that are greater than perchlorate, namely nitrate and thiocyanate. Cumulative risk assessment is commonly used by US EPA when evaluating pesticides, but has not been applied under the SDWA. The total effect on IUI can be estimated using perchlorate equivalence. The equivalence is based on affinity of the anion to the symporter. The study to determine equivalence has been conducted in cell culture using human NIS transfected into the cells (Tonacchera *et al.*, 2004). This is a reliable method that has been used for decades in medical pharmacology. Although some criticize cell culture as a substitute for human studies generally, in this case, the relative interaction between the anion and the receptor is better quantified *in vitro*. Additionally, multiple animal studies have reported similar potencies of the three goitrogens (Wyngaarden *et al.*, 1952; Wyngaarden *et al.*, 1953). Willemin and Lumen (2016) also published the development of a PBPK model to evaluate the dose-response of thiocyanate; thus, it is possible to increase the utility of the Model by introducing additional chemicals.

US EPA's Office of the Inspector General (OIG) released a report in 2010 recommending and demonstrating use of cumulative risk assessment for perchlorate, nitrate, and thiocyanate. They also included iodine deficiency as a thyroid stressor. The report noted that perchlorate accounted for less than 1% of total goitrogen load on the thyroid and regulation of this chemical in isolation would produce no benefit to public health. Other studies have also reported the same contribution of perchlorate to total goitrogen load (Tarone *et al.*, 2010; Bruce *et al.*, 2013).

Relatedly, the studies used to calibrate the model did not consider background doses of goitrogens. Only two studies were used to calibrate infant perchlorate, TT4, and fT4: Cao *et al.* (2010) and Leung *et al.* (2012). Cao *et al.* (2010) measured infant urinary nitrate, thiocyanate, and perchlorate, and reported geometric means and 95% confidence intervals for urinary nitrate of 95 μg/g creatinine (69-131) and urinary thiocyanate of 1000 μg/g creatinine (760-1320). In Leung *et al.* (2012), perchlorate, thiocyanate, and iodine were measured. For thiocyanate, they report thiocyanate levels of 373.5 μg/L (31.1–2420 μg/L) in maternal urine, and 193 μg/L (21.7–1880 μg/L) in infant urine (Leung *et al.*, 2012). The range that these two studies report spans two orders of magnitude suggesting significant variability in this study population. As a point of reference, NHANES 2011-2012 reports a geometric mean urinary thiocyanate and 95% confidence interval of 1133.5 μg/L (1002.1–1282.2) for females age 20 and older (Jain, 2016).

Thus, US EPA's calibration based on studies where the impact of another chemical with the same MOA also may be contributing to data reported is neither described as a limitation, nor considered in the assessment.

6.0 CONCLUSION

We have several scientific issues with the approach US EPA is taking to evaluate whether perchlorate should be regulated and at what level. In general we agree with the approach and process US EPA is taking as long as the process is transparent and science-based. We agree on the use of a BBDR or PBPK/PD model for the assessment of relevant physiological parameters that can inform US EPA on the possible health impact of perchlorate exposure. We agree that it must be scientifically defensible and utilize the best available science.

We think the US EPA Draft Model Report and BBDR Model Codes require considerable improvement to be useful for regulatory purposes. The Model Report can be improved with a more systematic approach and greater transparency. The Agency's cited literature will benefit by a complete literature review to support its conclusions.

The Model code must have greater transparency and resolve any inconsistencies. US EPA's choice of several parameters used in the model are not well supported or defined within the model code. The models are extremely difficult to set up and run. We have concern about the constraints of time on the peer reviewers to implement and critically review the model.

Finally, we have several overarching concerns that US EPA could address that would greatly assist a scientific peer review. The endpoint of hypothyroxinemia, despite the US EPA's recent SAB review, is not a scientifically robust endpoint for evaluation and other thyroidal parameters are necessary to determine an adverse effect. As hypothyroxinemia is not an adverse effect and US EPA has suggested it would relate this data to neurodevelopment in offspring, releasing any documentation related to the application of the model to neurodevelopmental outcomes is necessary. A full understanding of the model is contingent on understanding its intended use. Releasing this data allows for an understanding of the level of sensitivity required of the model. Finally, we do not understand how the peer reviewers will have the ability to conduct a thorough review given the limited time frame. We appreciate the additional 10 days, however, that still is insufficient to address the thoughtful and scientific approach one needs to evaluate any BBDR model.

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APPENDIX A

INTERTOX COMMENTS ON THE CHARGE QUESTIONS

INTERTOX

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U.S.A.

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October 21, 2016

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Delivered by email: perchlorate@versar.com

RE: PERCHLORATE CHARGE QUESTIONS

In response to the Federal Register Notice [81 FR 67350 (September 30, 2016)] and on behalf of the Perchlorate Study Group (PSG),[1] Intertox is pleased to submit comments regarding the charge questions.

Given that this is the first time EPA will develop a Maximum Contaminant Level Goal (MCLG) using Biologically Based Dose Response (BBDR) modeling and that the BBDR is complex, novel and potentially controversial, and will be influential, the PSG is committed to assisting EPA in its goal to use the best available science. The PSG has worked with EPA for more than 15 years to provide scientific information to derive and adhere to the basic standards of quality, objectivity, utility and integrity. It is with this spirit, Intertox provides comments on the peer review.

According to EPA's Peer Review Handbook (2015), there are two types of questions for an effective peer review. The first identifies technical and scientific issues on which the Agency would like feedback. The second invites broad evaluation of the overall work product.[2]

The EPA's charge questions are found here. Seven questions are included in the Draft Charge Questions.

Broad Evaluation Type Questions / Comments

None of EPA's seven listed charge questions addresses a broad evaluation of the BBDR work product and instead all questions listed are technical. The noticeable absence of these broader questions represents a substantial gap in the rigor of the peer review. The Draft Charge Questions would benefit greatly by the evaluation of this specific model for the purpose it is used.

One of the overarching concerns about a proper evaluation of a complex model is the magnitude of material a peer reviewer must go through, particularly given that most of the interim peer reviewers have no demonstrated PBPK/BBDR modeling experience. For example, there are two distinct models, each of which has thousands of lines of code and more than 500 variables. The model code was provided for use on two software platforms; however, one of these is no longer available, a scenario which further limits rigorous review of the model.

The peer reviewers should be asked to comment on the duration of time allowed for review as well as the adequacy of resources provided to review the literature database for perchlorate. We are concerned that EPA did not provide adequate time to conduct a comprehensive review of this model.

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[1] *The Perchlorate Information Bureau is supported by Aerojet Rocketdyne, American Pacific Corporation, Lockheed Martin and Orbital-ATK. These companies have worked cooperatively with the U.S. Environmental Protection Agency to increase scientific and medical understanding of perchlorate's risk to human health.*

[2] https://www.epa.gov/sites/production/files/2015-10/documents/epa_peer_review_handbook_4th_edition_october_2015.pdf

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It would be beneficial for peer reviewers to be given access to, and encouraged to read, the Agency's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*.[3] It would help the peer reviewers to understand how important data quality is to the Agency and provide guidance on addressing the charge questions it raises.

When a charge question asks, for example, "Does the developed model structure adequately and accurately describe the physiology…," what is meant by the term "adequately"? It would help the peer reviewers to understand the level to which they need to evaluate the model. There are many examples of these ambiguous phrases throughout the charge questions. Such undefined terms make it difficult for any peer reviewer to provide a consistent and thorough standard of assessment.

It is unclear why EPA is focused on the pregnant woman and fetus, lactating woman, and infant in exclusion of other life stages. Giving scientific rationale for this policy decision will be useful to the peer review panel as well as the general public. We note that using the results of the Agency's model to support this conclusion is insufficient evidence, as *the model itself* is at issue. Citing empirical evidence published in peer reviewed studies that directly compare adverse effects in these three life stages is the appropriate support.

Given the robust dataset for perchlorate, the Agency can also include a number of secondary sources of information from authoritative bodies should they need more information to address their questions. Notable examples that should not be overlooked include: National Research Council's 2005[4] evaluation of perchlorate and ATSDR's 2010 Toxicology Profile for perchlorate.[5]

Technical and Scientific Type Questions / Comments

Regarding the technical questions, there are topics EPA could expand on in its charge questions in order to ensure that the BBDR model is able to predict the physiology and pharmacology of perchlorate at low environmental doses. We have provided recommendations below:

- *Hypothyroxinemia as a clinical endpoint*. A clinician would test an individual for TSH and not necessarily test for free T4; additionally, hypothyroxinemia is not necessarily an adverse effect in a pregnant or lactating woman; to the point, the American Thyroid Association recommends *not* treating hypothyroxinemia. In the infant, hypothyroxinemia is also not recognized as an adverse effect that warrants treatment and there are no reference levels for this in infants. Is the model accurate to make predictions on health outcomes if the only output is fT4 (and total T4) rather than other relevant thyroid hormone parameters (i.e., TSH)? Explain the scientific support for only using fT4 and provide strong support for the exclusion of the other thyroid markers. The EPA is not a medical organization and the model developers are not clinicians, yet the output and interpretation of the model is to define disease. Does this model accurately predict disease in either the individual or a hypothetical population?
- *Exposure to other goitrogens*. EPA Office of Inspector General (OIG) has demonstrated that perchlorate accounts for less than 2% of the total dietary goitrogen load on a daily basis. How should the peer reviewers reconcile the fact that this model does not include nitrate and thiocyanate (as a minimum) in the model? How do peer reviewers assess the ability for the model to predict adverse outcomes on thyroid hormones given this limitation? Given the pharmacology and toxicology background of perchlorate and other goitrogens, can the model

[3] https://www.epa.gov/sites/production/files/2015-08/documents/epa-info-quality-guidelines.pdf
[4] https://www.nap.edu/catalog/11202/health-implications-of-perchlorate-ingestion
[5] https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=895&tid=181

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be further enhanced scientifically in a way that would improve the prediction capability?

- *Doses evaluated are not environmentally relevant.* There are no studies that demonstrate that perchlorate causes hypothyroxinemia in pregnant women, lactating women, or infants at any dose. Consider the doses in EPA's supporting document:
  - "…lactating mothers were predicted to become hypothyroxinemic or hypothyroid at 23 perchlorate exposures below 20 µg/kg/d, even with daily iodine intakes of 250 µg/d." The dose noted (20 µg/kg/d) would be equivalent to a water concentration of 746 ppb, assuming a body weight of 74.6 kg as EPA did in the BBDR model and a drinking water intake rate of 2 L every day).
  - "…the mother stays within the reference range during both pregnancy and lactation as long as perchlorate 14 exposures are below 4 µg/kg/d." Using the same assumptions, the dose of 4 µg/kg/d is equivalent to a water concentration of 149 ppb.

  The model does not predict a linear dose-response relationship. How do responses at high doses relate to doses EPA is considering for regulation? How does EPA reconcile that the doses in clinical studies are orders of magnitude higher than the doses that the model is being asked to use to predict fT4?
- Model predictions are not consistent with the known mechanism of action (MOA). The MOA for perchlorate has been well-recognized and undisputed for decades; that is, perchlorate reversibly blocks iodide uptake (iodide uptake inhibition; IUI) to the thryroid which, if significant (~75% IUI; NRC, 2005) and sustained for months, could result in a decrease in thyroid hormones (e.g., fT4). IUI is a non adverse effect and a clear precursor to an actual adverse effect; the accepted No Observable Effect Level (NOEL) for IUI is 7 µg/kg-d (Greer et al., 2002). Importantly, no other effects occur unless IUI occurs first. EPA should ask the peer reviewers to consider why its model predicts changes in fT4 at doses lower than those it predicts changes in IUI (via RAIU) and the recognized threshold for IUI in the literature.
- *Biological compensation and homeostasis.* What is the scientific assessment of the degree that the model incorporates homeostatic mechanisms? For example, what would the impact on the model be if it included up-regulation of the Sodium-Iodine Symporter?
- *Prediction of steady state is unrealistic.* Iodine and perchlorate intake fluctuate daily. What is the impact of the model output if the dose of perchlorate is steady-state versus the normal variable consumption of food and water?

Thank you for the opportunity to provide these comments.

Sincerely,

Richard C. Pleus, PhD
Intertox, Inc.

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APPENDIX B

INTERTOX COMMENTS ON THE LIST OF PEER REVIEW CANDIDATES

INTERTOX

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October 21, 2016

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Delivered by email: perchlorate@versar.com

RE: PERCHLORATE PEER REVIEW

In response to the Federal Register Notice [81 FR 67347 (September 30, 2016)] and on behalf of the Perchlorate Study Group (PSG)[1], Intertox is pleased to submit comments regarding the interim list of peer reviewers. We appreciate that EPA has opted to hold two peer reviews, the first for the Biologically Based Dose Response (BBDR) model and the second to evaluate the implementation of the model results to derive a Maximum Contaminant Level Goal (MCLG). Given that this is the first time that EPA will develop a MCLG using BBDR modeling, the PSG is committed to assisting EPA, as the PSG has for over 15 years, to ensure that the information it disseminates adheres to the basic standards of quality, objectivity, utility, and integrity. It is in this spirit that Intertox provides comments on the interim list of peer reviewers.

Given the compressed time frame for public comment, we have not attempted to evaluate or recommend individual peer reviewers. Instead, we offer general observations that we hope will add value as you develop your process.

Comment 1

Standards of information quality, the assessment factors, and guidelines for peer reviewers would assist the peer reviewers in developing the most reliable assessment for the Agency. These are key documents for the peer review process and provide a level of transparency in the quality the Agency seeks.

- Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (EPA Information Quality Guidelines).
- A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information
- This 4th edition of the Peer Review Handbook was developed by the U.S. Environmental Protection Agency (hereafter EPA or the Agency) to provide guidance to EPA staff and managers who are planning and conducting peer reviews.

The Agency might want to add additional documents, but these will benefit the peer reviewers with the understanding of the need for quality of scientific information as well as what constitutes "quality" scientific information. In the meantime, how will EPA substantiate its approach as an evaluation of a solid standard scientific assessment per the IAQ guidance on influential information?

[1] *The Perchlorate Information Bureau is supported by Aerojet Rocketdyne, American Pacific Corporation, Lockheed Martin and Orbital-ATK. These companies have worked cooperatively with the U.S. Environmental Protection Agency to increase scientific and medical understanding of perchlorate's risk to human health.*

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Comment 2

As stated in the FRN:

> Submit your comments on the interim list of peer review candidates and draft charge to Versar, Inc., no later than October 21,

And

> Questions concerning the interim list of expert peer review candidates and draft peer review charge questions should be directed to Versar, Inc.

The FRN states that this is an "interim list," but it is unclear the meaning of this term. Is it the intent of EPA or Versar to use the exact same peer reviewers for both peer review panels; will other peer reviewers be evaluated for the second panel; or will a subset be on both panels? Does EPA plan to look for additional experts to fill the subsequent peer review with another FRN?

Comment 3

Versar, Inc. assembled a panel of scientific experts to evaluate the draft BBDR model and draft report. EPA requests:[2]

> ...scientific experts whom [sic] have knowledge and experience in one or more of the following areas: (1) Physiologically-based pharmacokinetic (PBPK), physiologically-based pharmacokinetic/pharmacodynamics (PBPK/PD) and/or Biologically Based Dose-Response (BBDR) modeling, (2) fetal and neonatal thyroid endocrinology (clinical and experimental), (3) iodide homeostasis, and (4) perchlorate toxicology and mode of action or adverse outcome pathway.

This is a limited set of four categories of expertise. On June 3, 2016, EPA sought to expand the expertise since it had combined two peer reviews into one peer review. Because of that, EPA requested additional experts in one or more of the following areas of risk assessment to include:[3]

> An understanding of thyroid function (preferably in the sensitive life stages of interest), the importance of maternal thyroid hormone homeostasis in each stage of gestation, hypothyroxinemia, neurodevelopmental assessment indices for young children including the Bayley's Scale, the toxicity of perchlorate, epidemiological assessment techniques, and statistics.

Clearly the expertise required for the first and second peer reviews are different. A number of the experts in the interim list of 19 peer reviewers appears to fulfill the requirements of the second, but not the first. Will Versar or EPA explain how each of the current group of interim experts fills the categories of expertise requested currently and in March?

Comment 4

The Agency's Peer Review Guidance (2015) states:

> It [Peer Review] is conducted by qualified individuals (or organizations) who are independent of those who performed the work and who are <u>collectively equivalent in technical expertise to those who performed the original work (i.e., peers)</u> [emphasis added].

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[2] Federal Register (81 FR 10617; March 1, 2016)
[3] Federal Register (81 FR 35760; June 3, 2016)

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> Peer review is an in-depth assessment of the assumptions, calculations, extrapolations, alternate interpretations, methodology, acceptance criteria and conclusions pertaining to the scientific or technical work product, and of the documentation that supports them.

It is unclear what expertise was used to develop the model. If that information were made available, it would assist in obtaining the expertise necessary for this peer review. Additional expertise appears to be missing that would provide key insight to the evaluation of the BBDR model. How does the Agency envision that peer reviewers will assess the assumptions, calculations, extrapolations, *etc.* used by EPA, given the short time for the model review as well as the limitation on expertise? Additionally, to address possible issues of balance and quantity of work to be evaluated at least two, and preferably more, experts would fulfill each category. We suggest the interim list be expanded to include (but not be limited to) the following areas of expertise:

- Computer programming (two different platforms are offered; to evaluate the model codes); particularly experts in AcslX (Aegis Technologies) and R platforms (to provide guidance to experts on questions of software),
- Receptor pharmacology (to provide understanding of basic receptor ligand interactions relating to symporter function),
- Iodine regulation (clinical evaluations as well as iodine homeostasis, biochemistry, physiology, and lifecycle), and
- Statistical assessments (e.g., sensitivity analysis for BBDR models)
- Expert medical PBPK modelers (to compare the Agency's model with best available techniques and practice of modeling).

Comment 5

For this first peer review panel, it is unclear how the BBDR model code evaluation is expected to be conducted. Based on the biographies provided by the contractor, a number of candidates appear to have no experience with BBDR modeling. When they receive the model code, do Versar and EPA expect each panelist to download the model and run it prior to the public meetings? If not, why not? How does the Agency envision obtaining independent scientific advice regarding the model if the panelists cannot or do not run the model? How would EPA evaluate comments of a reviewer who has never run a model compared to a reviewer that has?

Thank you for the opportunity to provide these comments.

Sincerely,

Richard C. Pleus, PhD
Intertox, Inc.

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Public Comments

Submitted By

Environmental Defense Fund/

Natural Resources Defense Council

November 25, 2016

Russ Perkinson, (Mail Code 4607M)
Standards and Risk Management Division
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RE: Comments on EPA's draft Biologically Based Dose-Response Model and an accompanying draft model report; Docket No. EPA–HQ–OW–2016–0438

Dear Sir or Madam:

We appreciate the opportunity to comment on 1) EPA's draft Biologically Based Dose-Response Model (EPA 2016 Model) and 2) its accompanying draft model report entitled "Biologically Based Dose-Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses" (EPA 2016 Report) posted in the September 30, 2016 Federal Register and in Docket No. EPA-HQ-OW-2016-0438.

The EPA 2016 Model is designed to identify when the infant, breast feeding mother, pregnant mother and fetus have symptoms of hypothyroxinemia (low T4 thyroid hormone) but not symptoms of hypothyroidism (low T4 and elevated Thyroid Stimulating Hormone levels). Hypothyroidism is expected to result from sustained hypothyroxinemia. EPA's Science Advisory Board (SAB) concluded in 2013 that hypothyroxinemia is likely to harm the developing brain of a fetus or infant even if there is no evidence of hypothyroidism.

In essence, the SAB found that hypothyroxinemia is a more sensitive endpoint for fetal brain development than hypothyroidism. When hypothyroidism symptoms are seen, the harm to the fetal or infant brain is likely to be more severe.

For that reason, EPA's statement is particularly significant:

> The model predicts that a pregnant mother and a lactating mother at PND [post-natal day] 60 or 90 who only ingest 75 μg/d of iodine would be hypothyroid even without perchlorate exposure. With an iodine intake of 100 μg/d (considered medically insufficient), both pregnant and lactating mother would be barely within or just below the reference range.[1]

[1] EPA 2016 Report on page 7.

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While conversions between iodine intake and iodine in urine complicates the calculation, we estimate that 20% of pregnant women have iodine intake levels than low enough (< 100 μg/day) to result in hypothyroidism with any exposure to perchlorate.[2]

The statement is even more significant when considering:

- Hypothyroidism is not the most sensitive endpoint. The percentage of pregnant women who cannot tolerate any exposure to perchlorate would be greater if hypothyroxinemia were considered.
- The Food and Drug Administration (FDA) has already demonstrated that most of the food and beverages we consume are contaminated with perchlorate. In 2008, it estimated that women of childbearing age are already exposed to 0.09 to 0.11 μg/day of perchlorate in the diet.[3] This estimate does not consider perchlorate in drinking water.
- The model does not consider the concurrent exposure to nitrates or thiocyanates in the diet. These two other chemicals impair the same iodine uptake mechanism affected by perchlorate. Therefore, the percentage of pregnant women at risk of harm to the fetus would be even greater.

Regarding the EPA 2016 model itself, we think it is a significant improvement over the hypothyroxinemia model proposed by Lumen et al[4] (Lumen 2013 Model) on which it is based and look forward to seeing the results of the external peer review.

However, we have serious concerns that the model does not address the first and second trimesters of pregnancy. Analysis on only the third trimester, when the fetus has a functioning thyroid, falls short of what the SAB recommended. In the first trimester, the fetus has no thyroid and depends on the maternal circulation for an adequate supply of T4, a hormone that is essential to brain development. With two functioning thyroids (the fetus' and the mother's), each with its own reserves of T4 – the situation in the third trimester addressed by the model – appears to be less risky than in the first trimester.

We maintain that in setting an MCLG EPA must consider the impacts on a pregnant women's fetus during the first two trimesters and on pregnant women with serious iodine deficiency and hypothyroidism pursuant to §1412(b)(3)(C)(i)(V) of the Safe Drinking Water Act. The provision states that EPA should consider:

> "The effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals

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[2] The most recent assessment was published by Caldwell KL, Pan Y, Mortensen ME, et al., Iodine status in pregnant women in the United States: national Children's study and national health and nutrition examination survey. Thyroid. 2013;23:927–37. It stated that 26.3 % of pregnant women have urinary iodine concentrations below 100 μg/L, and 15.7% have levels below 50 μg/L. In estimating that 20% of pregnant women, we assumed that urinary iodine levels are 75% of intake.

[3] Murray C.W., Egan SK, Kim H, Beru N, Bolger PM, US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and iodine. Journal of Exposure Science and Environmental Epidemiology (2008) 18, 571–580.

[4] Lumen A, Mattie DR, Fisher JW. Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model. Toxicol Sci. 2013 Jun;133(2):320-41.

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with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population."

This omission, which the agency states in a follow-up email is due to data limitations, means that the life stages of greatest risk are not modeled. EPA should specifically ask the expert reviewers to consider the implications for the model's relevance. As EPA moves forward with perchlorate drinking water regulations, this shortcoming must be addressed

We discuss these issues in more detail in Attachment A.

In summary, EDF and NRDC believe that EPA's model is a useful step forward in the development of a maximum contaminant level for perchlorate in drinking water. However, it leaves important issues unresolved. The agency must resolve these issues as it completes this step and undertakes the next step in the process.

We appreciate the opportunity to comment, and if you require any additional information, we can be reached at 202-572-3263 or tneltner@edf.org and jsass@nrdc.org.

Sincerely,

Tom Neltner
Chemicals Policy Director
Environmental Defense Fund

Jennifer Sass, Ph.D.
Senior Scientist
Natural Resources Defense Council

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Attachment A
Responses to NRDC's Concerns with Lumen Model

In February 28, 2014, the Natural Resources Defense Council (NRDC) identified six recommended improvements to the Lumen et al. 2013 model that was under consideration for a biologically-based, dose-response model (Lumen et al 2013). On March 24, EPA's Eric Burneson, Director of Standards and Risk Management Division, Office of Water, provided feedback from those responses. The recommendations and the responses are described below

1. **Expand the model to include the first two trimesters in addition to infants. The current model is based only on the end of the third trimester when the fetus has a functioning thyroid.**

EPA Response in March 2014: We agree that there is good reason to include at least the first trimester in the modeling because the adverse effects of maternal hypothyroxinemia are thought to be initiated during that period. We are evaluating the existing body of data to see if adequate information is available to consider this sensitive life stage.

EDF & NRDC Comment: According to an October 28, 2016 email to EDF from EPA, the agency did not model hypothyroxinemia the first two trimesters despite agreement that the adverse effects of maternal hypothyroxinemia are thought to be initiated from the first trimester. EPA indicated that there was not adequate information to consider these sensitive life stages for two reasons:

- Free T4 levels in the 1st and 2nd trimester pregnant women were not modeled due to a lack of available published (peer reviewed) data
- Almost no data on the functioning/parameters of the fetal thyroid in those trimesters (after it develops). Apparently, the model for the third trimester uses factors extrapolated from the newborn infant.

We appreciate EPA's prompt response to our request and were surprised that such a critical limitation was not made explicit in the report. Our understanding is that in the first trimester, the fetus does not have a functioning thyroid. So there should be no need to model its production of thyroid hormones. In the absence of reliable data on the 2.5th and 10th percentile of free T4 levels in the first trimester, it seems reasonable to assume that maternal hypothyroxinemia in the first trimester would adversely affect fetal brain development.

In the absence of such critical information, we recommend, at a minimum, that EPA:

- Make the data gap explicit to the external peer reviewers and ask that they comment on EPA's approach to neither model this risk, nor to adjust for it with uncertainty factors.
- The final MCLG should include additional safety factors to protect fetal brain development during the first two trimesters
- EPA should revisit the issue in its six-year review of the standards.

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2. **Ensure the model considers iodide levels at the 95th and 99th percentiles of pregnant women, not just the 90th percentile.**

EPA Response in March 2014: We intend to consider a range of iodide levels as we model perchlorate impacts. We are currently evaluating the literature to determine the range of dietary iodide levels for which thyroxin levels are known. We will consider the impact of extrapolating to low levels of iodide ingestion on model performance if these data are not available.

EDF & NRDC Comment: The model considers only iodine intakes as low as 75 μg/day just as the Lumen et al 2013 model did, and thus EPA's model unfortunately provides no improvements in this regard.

3. **Reevaluate affinity constants for iodide and perchlorate to ensure they are based on a robust data set and are calculated consistently.**

EPA Response in March 2014: We recognize the uncertainty in affinity constants for perchlorate and iodide for the sodium iodide symporter (NIS). We will evaluate the feasibility of conducting a sensitivity analysis to investigate the effect of changes in affinity constants on model outputs.

EDF & NRDC Comment: According to footnote 2 in the report

> "As detailed in this report, the affinity of perchlorate for the sodium-iodide symporter (NIS), a key parameter in the PBPK/BBDR models, was revised based on a re-evaluation of original data. The revised value was substituted into the model of Lumen et al. (2013) in the analyses conducted here." *Footnote 2 of report.*
>
> "Based on re-evaluation of the in vitro data of Kosugi et al. (1996), the affinity constant (Km) for binding of perchlorate to the NIS (KM_TPNG) was reduced from 1.6×10^5 ng/L (McLanahan et al., 2014; Clewell et al., 2007; Merrill et al., 2005) to 6×10^4 ng/L (Schlosser, 2016). This lower value was shown to provide model predictions much more consistent with the radioiodide uptake inhibition data of Greer et al. (2002) for doses up to 100 μg/kg/d than those obtained with the former value for the Km." *Page 45 of report.*

We appreciate EPA's revisions to the Lumen model. They appear to address our concerns.

4. **Incorporate thiocyanate and nitrate in the model as recommended by EPA's Science Advisory Board since they also inhibit iodide uptake in a manner similar to perchlorate.**

EPA Response in March 2014: EPA's current focus is to develop a PBPK model in accordance with the recommendations of the SAB. We recognize that co-exposures to thiocyanate and nitrates (as well as other thyroid hormone disruptors) are likely occurring in the U.S. population. We will strive to address this issue to the extent possible given the current state of the science.

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EDF & NRDC Comment: Nitrates and thiocyanates do not appear to be considered in any way in the model despite evidence that they also interfere with the same symporter affected by perchlorate.

EDF and NRDC maintain that EPA cannot ignore the cumulative effects of nitrates and thiocyanate on the transport of iodine into the thyroid. Pursuant to Section 1412(b)(4) of the Safe Drinking Water Act (SDWA), the Maximum Contaminant Level Goal (MCLG) "shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." If nitrates are in drinking water, they will increase the impact of perchlorate. To fulfill its responsibilities under the law, the safe level of perchlorate needs to be adjusted downward to address the contribution of nitrates and thiocyanates.

In addition, SDWA section 1412(b)(3)(C)(i)(VII) would require the agency to consider the impact of nitrates and thiocyanate as another relevant factor. At a minimum, EPA must add a safety factor to account for the presence of nitrates and thiocyanate in the water and the diet.

5. **Justify the selection of 10 pmol/L of maternal free T4 as the threshold for hypothyroxinemia.**

EPA Response in March 2014: Although Lumen et al. (2013) used a target value of 10 pmol/L for free T4, EPA has not yet determined the target levels for hypothyroxinemia for different life stages in the current modeling effort.

EDF and NRDC Comment: Based on our understanding of the model, EPA uses free T4 levels between 2.5th and 10th percentile to define hypothyroxinemia. When free T4 levels fall below the 2.5th percentile, hypothyroidism would be dominant. While hypothyroidism is a less sensitive endpoint, it indicates that there is a sustained reduction in production of T4 and the T4 reserves are too low. Therefore, the risk to fetal and infant brain development is greater.

The EPA 2016 model predicts that a pregnant women would suffer hypothyroxinemia when the free T4 levels are between 10.6 to 11.7 picomolar. In infants, the levels vary with post-natal days. As noted above, there are no estimates for fetuses.

We appreciate EPA's 2016 update of the Lumen et al 2013 model with this more science-based approach. We assume the external peer reviewers that EPA has selected will have an opportunity to evaluate the new model and comment on the merits of EPA's approach.

6. **Compare the model results to NHANES monitoring data**

EPA Response in March 2014: EPA is considering how best to validate the model outputs. We appreciate and will give consideration to your recommendation to compare the model results to the NHANES monitoring data.

ED_005043_00062728-00131

EDF & NRDC Comment: We appreciate EPA's efforts to update its model using the latest NHANES monitoring data.

Public Comments

Submitted By

Gradient

GRADIENT

November 25, 2016

Mr. Joel Beauvais
Deputy Assistant Administrator
U.S. Environmental Protection Agency
Mail Code 4101
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Submitted via: http://www.regulations.gov

RE: Comments Submitted by Gradient on Docket No. EPA-HQ-OW-2016-0438: Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses

Dear Mr. Beauvais:

Gradient appreciates this opportunity to submit comments on EPA's draft report concerning the development of a biologically based dose response model for the effect of perchlorate on thyroid hormones on vulnerable populations.[1] Gradient has been involved with human health risk assessment for over 30 years and has extensive experience evaluating physiologically based pharmacokinetic modeling of goitrogens in the context of quantitative risk assessment.

We would like to commend EPA and the report authors for the extensive amount of work done in adapting and expanding on earlier perchlorate modeling efforts. The work summarized in the report is an important advance in the field of biologically-based dose response models, particularly the focus on addressing multiple potentially sensitive subgroups. The ultimate purpose of this work is to create a model that will be used to establish a safe exposure limit for perchlorate. If a model is used for such an application, it is important to clearly describe its assumptions and limitations so that downstream users do not over interpret the model's results. A model used in this way should ideally also be able to describe (even if in general terms) the full extent of goitrogen exposure that the target population will experience. Our specific comments related to these concerns are provided below. We note that many of these comments are consistent with the draft charge questions proposed for the expert panel review.

Comments

Failure to address other goitrogens

1. The EPA modeling report document makes no mention at all of the potential impacts of thiocyanate (SCN) and nitrate (NO_3) on the thyroid and thyroid hormone synthesis. This is not reasonable given that it is known, from multiple scientific studies, that SCN and NO_3 also impact thyroid activity. For example, the Cao *et al.* (2010)[2] study that EPA repeatedly cites in the report found that all three ions were associated with increased urinary TSH in infants exposed to these ions during the first year of life, and that the associations with SCN and NO_3 were observed regardless of iodine status whereas perchlorate's effects were only observed in the low iodine status subgroup (*i.e.*, < 100 μg/day iodine excretion, a situation where the current model is said to be unreliable). Moreover, the multivariate

[1] Gradient is submitting these comments in conjunction with SQM, a manufacturer of fertilizers and other products.
[2] *Environ Health Perspect.* 2010. 118(9): 1332–1337

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model coefficients were larger for SCN and NO_3 compared to perchlorate, indicating they were stronger predictors of TSH.[3] This is consistent with modeling work we haveconducted with the earlier perchlorate model which showed that the NIS inhibiting effects of dietary SCN and NO_3 exposures could dwarf potential exposures to perchlorate.[4] The inability of the current model to address the impacts of these two ions (which are both present at substantial levels in the diet) should, at a minimum, be pointed out as a source of model uncertainty and a need for future research. EPA should consider and discuss how a recent PBPK model of thiocyanate kinetics could be incorporated into the modeling effort (Willemin and Lumen, 2016).[5] The current model's inability to address the impact of other goitrogens (not only those that affect NIS but also others such as soy components) is an important limitation because low level, variable exposures to these chemicals are clearly tolerated in the human population.

2. p. 39. *"The mammary gland is capable of concentrating iodide in breast milk via the sodium iodide symporter (NIS), a membrane bound transport protein that is under the control of prolactin and other hormones (Micali et al., 2014; Semba and Delange, 2001). There are likely several mechanisms involved, including other transporters such as pendrin, but data by which their contribution to iodide transport could be quantified (vs. that of NIS) is lacking. Therefore the model structure only includes NIS-mediated transport between blood plasma and breast milk."*

   Given that the modeling indicates that the lactating woman and the breastfed infant are key sensitive populations, this failure to include other mechanisms of iodine transfer into breast milk is an important area of uncertainty. In Figure 7 (bottom graph, perchlorate), the model predictions appear to approximate the Leung *et al.* (2012)[6] data but, due to the log scale, may in fact inaccurate by several fold. In the corresponding iodide graph (Figure 7, top), the model is clearly over predicting breast milk iodide concentrations. It is unclear why only the Leung *et al.* data are used for comparison. Several other breast milk iodide data sets are available (Kirk *et al.*, 2007; Bruhn and Franke, 1983; Pearce *et al.*, 2007).[7] EPA acknowledges the uncertainty when they later note: *"The range of iodide concentrations in spot breast milk samples can exceed two orders of magnitude, so factors other than variation in dietary intake must influence this range."* The potential impact of other goitrogens is an important concern here.

<u>Failure to address compensation/adaptation</u>

3. The EPA report does not address possible compensation/adaptation in response to decreased T_4 that is insufficient to trigger an increase in TSH above a defined clinical definition value (*i.e.*, hypothyroxinemia *vs* hypothyroidism). Does EPA have any data supporting the idea that no compensation/adaptation occurs until the hormone profile is consistent with hypothyroidism? We could find no data indicating a lack of compensation (alterations in NIS activity, hypertrophy of follicular cells, delayed elimination of T_4, *etc.*) during hypothyroxinemia. This seems to be intuitively problematic given that humans have evolved to respond to slight perturbations in iodide availability as goitrogen intake varies from day to day. A study by Wei *et al.* (2013)[8] reports that a hypothyroxinemia-inducing diet in rats did induce compensatory actions (*e.g.*, increased NIS expression) but unfortunately the authors did not measure TSH so it is unclear whether the rats were truly not hypothyroid. Clearly if some degree of compensation occurs even in hypothyroxinemia, this would need to be addressed in the model. Because the model is entirely premised on the

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[3] SCN was also a more important predictor of T_4; perchlorate and NO_3 had similar coefficients.
[4] Society of Toxicology Annual meeting, 2015. Abstract 727.; Society for Risk Analysis meeting, 2015, Abstract M2-H.4.
[5] *Toxicol Appl Pharmacol.* 2016. 307:19-34
[6] *Thyroid.* 2012. 22: 938-943.
[7] *Environ Health Perspect.* 2007. 115(2):182-6; *J Dairy Sci.* 1983. 66(6):1396-8; *J Clin Endocrinol Metab.* 2007. 92(5):1673-7
[8] *Int J Environ Res Public Health.* 2013. 10(8): 3233–3245

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absence of any compensation during hypothyroxinemia, the impacts of exposure to perchlorate and other goitrogens could be overestimated.

4. p. *16 "In the range of evaluation, it is assumed that there is insufficient feedback control of the T4 concentrations on TSH levels to warrant model description."* Is there insufficient feedback or no feedback? If insufficient, how was this judged? As noted above, this is a critical assumption in the model, *i.e.*, that no compensation or adaptation occurs when an individual becomes hypothyroxinemic. No empirical support is given for this assumption and a more robust defense of this assumption is needed.

<u>The pregnancy model does not address early gestation</u>

5. Multiple studies indicate that the developing fetus is most sensitive to hypothyroxinemia in early gestation and some studies have indicated that hypothyroxinemia in later gestation may not pose risks (Negro *et al.*, 2011).[9] The EPA model (like the earlier model on which it is based) is not a true dynamic model of pregnancy but rather a model of a specific time point late in gestation (*i.e.*, the model considers a woman and a near term fetus but does not include equations describing the growth of the fetus and corresponding maternal changes over the course of pregnancy). How can one reconcile the modeling of only the late stage fetus when studies suggest the early stages of pregnancy are more critical? Furthermore, what does the suggestion that the late stage fetus is relatively more resistant to the effects of maternal hypothyroxinemia than the early stage fetus say about the relative sensitivity of the neonate, in which the thyroid is even more mature? We could find no studies addressing the neurodevelopmental impacts of lactational exposure alone; the sensitivity of the post-natal infant is only inferred from the demonstrated sensitivity to *in utero* exposures (again, typically early in gestation).

<u>Consider the use of probabilistic models</u>

6. EPA should consider using or commenting on the probabilistic version of the perchlorate BBDR model developed by Dr. Annie Lumen (Lumen *et al.*, 2015; 2016).[10,11] This newer code allows for the use of distributions for key model inputs (*e.g.*, maternal perchlorate and iodine dose, drinking water intake) which may provide a more informative prediction for making policy decisions (*i.e.*, in terms of expressing uncertainty *via* a distribution of predicted results). This type of model would also help to better characterize model uncertainties.

<u>Interpretation of Aboul-Khair *et al.* publication on thyroid function during pregnancy</u>

7. p. 38. *"Urinary excretion of iodide was found to decrease over time in 7 lactating women (Aboul-Khair et al., 1964) for postpartum weeks 2, 6 and 12. The urinary iodide excretion clearance values (L/h) and the estimated urinary iodide excretion clearance value from the 3rd trimester mother at birth (Lumen et al., 2013) were used for the lactating mother model for iodide. In a similar trend, the calculated thyroidal uptake of iodide declined over 12 weeks of lactation (Aboul-Khair et al., 1964).*

   A review of the Aboul-Khair study[12] indicates that renal clearance between weeks 6 and 12 post-partum was not significantly different (37.1 ± 2.88 ml/min *vs.* 34.97 ± 2.02 ml/min). Was this time period treated as a constant value in the modeling? Moreover, this very important indicator of maternal iodide kinetics on PND 7 (the day of greatest sensitivity according to the model) is based

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[9] *Endocr Pract.* 2011. 17(3): 422–9
[10] *Front Pharmacol.* 2015. 6:107
[11] *Toxicol Appl Pharmacol.* 2016. 314:24-38
[12] *Clin Sci.* 1964. 27:195-207

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on an interpolation between PND 0 (based on the Lumen *et al.* model) and PND 14 (based on the Aboul-Khair study). The data supporting this model parameter are very limited and it would be useful to explore this *via* a sensitivity analysis. In addition, the change in iodide uptake by the thyroid in the Aboul-Khair *et al.* study was described by the authors as not significantly different across the post-partum period studied (26.93 ± 2.93, 22.32 ± 2.60, 21.87 ± 2.22 at 2, 6 and 12 weeks, respectively). Why did the EPA apparently address this parameter as declining over time? How does the decision to model a non-statistically significant change as if it were a real difference impact the model predictions?

Need to clarify what is adverse

8. The modeling appears to indicate that the lactating mother (and possibly the pregnant mother) are the most sensitive groups relative to hypothyroxinemia and that the breast fed (and bottle fed) infant are actually less sensitive (*i.e.*, only becoming hypothyroxinemic at higher perchlorate doses, lower iodine intakes) than the mothers (EPA, page 7). The concern about maternal hypothyroxinemia is the effect on the nursing child but the modeling seems to suggest that some level of maternal hypothyroxinemia may not be adverse to the infant (this is implied by the text but never stated). This will complicate the establishment of a thyroid hormone decrement that is considered adverse.

9. p. *17 "Given the lack of a unified clinical definition, for the purpose of this report it is assumed that euthyroid conditions occur for fT4 levels between the 10th and 90th percentile of the entire population in a given life stage, and that hypothyroxinemia occurs for fT4 levels between the 2.5th and 10th percentile for the entire population. When fT4 falls below the 2.5th percentile for the entire population in a life stage, it is assumed that TSH levels would be sufficiently elevated to trigger hormonal feedback, invalidating the model predictions. While model simulation results are shown beyond this range for the purpose of illustration, simulation curves for these results 18 are shown in grey (vs. black) to indicate that the confidence in those model predictions is low (e.g., Figure 10. Free T4 (fT4) levels as a function of perchlorate exposure and dietary iodine ingestion in the gestation-week 40 pregnant mother and fetus."*

   First, we appreciate that EPA is making an effort here to indicate where the model is considered unreliable. While the fT4 population distribution percentages used by EPA to characterize hypothyroxinemia (*i.e.*, 2.5% to 10%) seem to be consensus values, the actual fT4 concentrations (in nM), which are needed to compare to model predictions, seem open to debate (Moleti *et al.*, 2011).[13] Will an agreement on what level of fT4 decrement is adverse be required in order to use the model to establish a reference dose? Would a probabilistic analysis of this cutoff value be helpful?

Need to be transparent on model validation and precision

10. Calibration studies of the model (Figures 4-9) seem to suggest the model is "in the ballpark". That is, when the model is run using a range of iodine intakes (75 to 250 μg/day) the outputs as a whole are in the order of magnitude range of the results reported in epidemiology studies. This suggests the model is accurate but is not very precise. That is, the model may not be able to reliably distinguish a safe level of exposure of for example, 4 μg/kg-day vs 12 μg/kg-day.[14] EPA should be very clear about the model's predictive precision. All too often, policy makers impute much more precision to models than they actually deserve.

11. EPA should consider conducting a multivariate sensitivity analysis. An extremely large number of model parameters are either fit values or referenced to prior modeling efforts (where they were also

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[13] *J Thyroid Res.* 2011. 463029

[14] These values are used to illustrate the comment but do not represent actual model generated values or measured precision of the model.

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fit values). Thus many of the key inputs are not based on study data for that particular value but were chosen because they seem to work in the model. While this is not unusual, multiple combinations of different input values could equally lead to the same results.

12. p. 17, *"The actual range of model accuracy is uncertain, due to the fact that the data on urinary and breast milk iodide levels, and TH blood levels, are generally not correlated with specific iodine intake levels (doses). Hence model predictions of fT4 as a function of iodine dose cannot be evaluated or calibrated against corresponding dose-response data."* It would be helpful to acknowledge this uncertainty in the executive summary.

13. p. 18 *"the model predictions are likewise judged to be reliable for ≥ 150 μg/d iodine, but to have increasing uncertainty at 100 μg/d iodine (where maternal fT4 approaches the bottom of the reference range)"* Does this mean that the model should only be used to set acceptable perchlorate intakes where the iodine intake is 150 μg/d or higher? This would have an important impact on the use of the model.

Do the model predictions match existing data?

14. p. 8. *"The model predicts that a pregnant mother and a lactating mother at PND 60 or 90 who only ingest 75 μg/d of iodine would be hypothyroid with no perchlorate exposure."* A review of the available epidemiology data indicates this prediction is neither supported nor contradicted by the data. There are surprisingly few studies examining the correlation between urinary iodine concentrations and thyroid parameters and even fewer that find an effect of iodine insufficiency on such parameters among pregnant and lactating women. We note a recent study by Liu *et al.*[15] reported that even in an iodide deficient population of lactating women (75th-tile urinary iodide = 73.65 μg/l), only a small percentage (3.77%) of subjects were hypothyroid and only 17% were said to be hypothyroxinemic. EPA should include a discussion of how well the model prediction is matched by actual data as a matter of transparency. More broadly, this is a very complex model with many inputs and predictions. It would be helpful to include a table of model predictions (*i.e.*, maternal urinary iodide, breast milk perchlorate, *etc.*), the data sets to which they are compared, and a general statement of the degree of precision and accuracy.

EPA modified the NIS inhibition parameters of perchlorate to better fit experimental data

15. p. 45. The report describes how EPA changed the Michaelis-Menten values for NIS inhibition by perchlorate based on a re-analysis of Kosugi *et al.* (1996) (described in more detail in the appendices).[16] Although not directly addressed in the report, it appears that EPA has effectively doubled the potency of perchlorate as an inhibitor of NIS iodide uptake relative to what was reported by Tonacherra *et al.* (2004).[17] The results of Tonacherra *et al.* are also consistent with what can be obtained from Greer *et al.* (1966), Wyngaarden *et al.*, (1953) and Alexander and Wolff (1966).[18] While it is reasonable to reanalyze older data using more sophisticated methods, if EPA's assessment of perchlorate's NIS inhibiting potency is inconsistent with multiple prior studies, this needs to be explained. As a matter of transparency, the relative potency of iodide, perchlorate, SCN and NO_3 is familiar and well understood to the broader audience. It would be helpful for EPA to incorporate this concept into the discussion.

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[15] *Br J Nutrition*. 2015. 114, 1487–1495
[16] *Biochem Biophys Res Commun*. 1996. 227(1):94-101
[17] *Thyroid*. 2004. 14(12):1012-9
[18] *Endocrinology*. 1966. 79(2):237-47; *Endocrinology*. 1953. 52(5):568-74; *Endocrinology*. 1966. 78: 581–590.

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More explanation is required on why the BBDR model does not address the first few days of life

16. p. 21. *"Changes in TH kinetics have been noted in the first few days after birth (Fisher and Klein, 1981; Jacobsen et al., 1977; Erenberg et al., 1974; Abuid et al., 1973)."* The modeling as described in the report only focuses on PND 7. Did EPA attempt to model earlier time points? Were there no data to support assumptions?

Points concerning clarity of the text or need for additional discussion

17. p. 7. In the summary on page 7, why does EPA focus on perchlorate exposures below 20 μg/kg-day when the existing RfD is 0.7 μg/kg-day? The wording used is vague: "the lactating mothers were predicted to become hypothyroxinemic or hypothyroid at perchlorate exposures below 20 μg/kg/d, even with daily iodine intakes of 250 μg/d." Why not indicate the exposure level where hypothyroxinemia did not occur, which is the value of ultimate interest?

18. p. 7. *"the lactating mothers were predicted to become hypothyroxinemic or hypothyroid at perchlorate exposures below 20 μg/kg-day."* EPA is been very clear that the model is not reliable in the range associated with a hypothyroid condition, therefore the prediction cannot distinguish between hypothyroxinemia and hypothyroidism.

19. p. 11. "*Thus adverse effects of moderate postnatal thyroid hormone decrements (hypothyroxinemia) on neurodevelopment in full term (born healthy), nursing or bottle-fed infants have not been studied. However, as described in a detailed review by U.S. EPA (2012), a reduction in the storage of thyroid hormone and iodine, as well as rapid thyroid hormone turnover (i.e., shorter half-life) in the fetus, neonates and children makes these life stages more sensitive to thyroid disrupting agents such as perchlorate compared to adults. Furthermore, the physiological demand for thyroid hormones is far greater in the developing fetus, neonate and child compared to the adult, again increasing the vulnerability to thyroid disrupting agents."*

    EPA acknowledges that the key efects they are concerned with have not been demonstrated in the literature (as concerns neonatal exposure). EPA then cites their own prior logical argument as support for this concern. This seems rather weak support for such a critical aspect of the work.

20. p. 12. EPA states that Fisher *et al.* (2016)[19] and SAB (2013)[20] provide strong support that the infant is particularly sensitive to perchlorate exposure. The Fisher *et al.* paper describes an earlier version of the same model EPA is discussing. So essentially the argument is that the current model needs to be concerned about infants because the model shows infants to be susceptible. That is rather circular. The Fisher *et al.* paper only discusses perchlorate in the context of it having been a focus of earlier models. Furthermore, although the Science Advisory Board did direct EPA to consider infants as a vulnerable population group, they also noted: "Although adverse neurodevelopmental effects of perchlorate in infants and children have not been reported in the literature, the risk of adverse effects can be reasonably inferred from perchlorate's mode of action and the known role of thyroid hormone on human brain development." (p.2) We agree that the SAB's reasonable inference is valid but are skeptical that an inference where study data are lacking can be called *strong* support.

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[19] *PLoS One*.2016 11(3):e014930

[20] "SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate." EPA-SAB-13-004

21. p. 13 (bottom of page). EPA states that the lactating mother and neonate are the most sensitive subpopulations but earlier stated that it is not clear whether the pregnant woman or lactating woman are more sensitive. The discussion should be consistent.

22. Figure 2 is a bit confusing with the volume of distribution (Vd) shown separate from the biological compartments (with which it is synonymous). EPA might consider an explanation as to why Vd is shown separately.

We request that EPA and the expert panel consider the points noted above in finalizing the model, which will be a critical tool for setting safe exposure levels. We appreciate the opportunity to provide this input.

Sincerely,

Gradient

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ED_005043_00062728-00140

Public Comments

Submitted By

NASA

November 25, 2016

EPA-HQ-OW-2016-0438
Air and Radiation Docket
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460-0001

Subject: Request for Public Comments To Be Sent to EPA on Peer Review Materials To Inform the Safe Drinking Water Act Decision Making on Perchlorate [81 FR 67350, September 30, 2016]

NASA thanks EPA for the opportunity to provide comments, issues, and requests during the public comment period for the proposed Perchlorate model. NASA reviewed the proposed model and identified procedural, as well as, general and specific technical issues summarized below. These comments are intended to target gaps and approaches, which if addressed, will improve the efficacy and applicability of the model used in the development of an MCL for Perchlorate. NASA supports sound science as a foundation for regulatory action and appreciates EPA's consideration of this and all other input during the public comment period.

NASA requests EPA address specific procedural issues that impacted on the ready identification of scientific and technical issues during this review process. Independent, rigorous peer review provides the best method to consider and address emerging scientific or technical disagreements. EPA's decision to separate the draft peer review charge questions from the public comment review of the model hampered the reviewer's ability to link issues with the model with the crucial direction provided to the peer review process. The peer review charge questions were subjected to a shorter comment period with EPA providing little clear direction on how specific critical issues identified in the actual review of the proposed model, in subsequent public comment, would be considered during peer review.

In addition, EPA stated that its contractor, Versar, would summarize the public comments that would be shared with the peer reviewers. Such an approach limits the peer reviewers' ability to see the depth and range of public comments for consideration This practice is contrary to the open and complimentary provision of all public comments for reviewers. Independent, rigorous peer review provides the best method to consider and address emerging scientific or technical disagreements. Versar would also summarize the peer reviewers' comments and draft the final peer review report. Generally, an independent peer review report is drafted by the participating members. EPA's approach with the lack of clear direction, support for open sharing of information and the peer reviewers' control over their deliberations presents a troubling approach that threatens to cripple the independent and informed nature of peer review for the proposed Perchlorate model. Also EPA has not indicated how the proposed peer review of the model would be considered. EPA is silent on whether the peer review serves as a majority report, delineating next steps or simply a collection of opinions (often referred to as a letter report) for EPA to consider. NASA again stresses the value of a rigorous, independent peer review to address outstanding scientific and technical issues in the development of sound policy and

regulatory actions. We request EPA provide clear direction and transparency for a robust and effective peer review of the proposed Perchlorate model.

NASA also submits comments on scientific and technical issues identified in the review of the proposed Perchlorate model. This review serves to raise major issues to EPA with the request for response or the incorporation of outstanding issues into the peer review process for appropriate resolution.

Primarily, NASA notes the significant contributions and technical expertise for PBPK modeling of Perchlorate provided to EPA by Food and Drug Administration (FDA) and Department of Defense (DoD) scientists and researchers. We strongly suggest EPA give focused consideration to the technical issues raised by these experts in the FDA and DoD public comments. In a unique partnering effort, EPA collaborated heavily with these experts in various phases of the development of the proposed model. In support of the previous interagency collaboration, NASA concurs with DoD and FDA on the scientific and technical issues identified during this public comment period. We request EPA address outstanding gaps, issues, or need for clarification or validation contained in the expert input found in FDA and DoD comments.

NASA identifies additional areas of concern. The first major issue is EPA's fundamental assumption of using hypothyroxinemia as the end point. NASA understands that the SAB took this very conservative approach to target a specific condition not directly associated with a health impact. However, EPA's use of this endpoint in the proposed model lacks any substantiation in the available literature, especially for critical criteria, such as the Mode of Action (MOA), links to a disease state, or key thyroid endpoints. Additional questions arise over the relationship between EPA's estimation of Perchlorate exposure and the likely relevant Perchlorate exposures. EPA is strongly encouraged to request peer review and suggested approaches to strengthen the proposed model, based on expert opinion and alternative literature-supported approaches, especially in the consideration of the roles of TSH, T3, fT4 hormones on the impacts on the thyroid in the presence of Perchlorate. The proposed model serves as the basis for far-reaching regulation and would greatly benefit from rigorous, scientific reflection of the peer-reviewed literature.

Second, NASA's review identified the need for formal calibration of the proposed model, crucial steps to ensure scientific integrity. EPA notes that the proposed model is calibrated (refer to Pages 27-29 and 60-68) but lacks documentation to support this fundamental step. EPA needs to provide this documentation to the peer review panel for consideration and should make this determination public in the peer review report.

Third, an independent evaluation and validation of the model is critical to truly understanding the strengths, weaknesses and opportunities to improve the model in application. Questions over the proposed model's ability to track with results in existing literature further fuel the need for an independent validation. Currently EPA does not expressly request, via the proposed charge questions, that the peer reviewers conduct model validation but should expand the peer review charge questions to explicitly ensure model validation with substantiating documentation.

Fourth, EPA incorporated numerous assumptions and alternative approaches throughout the proposed model. Among these assumptions are contentious issues, such as its consideration of sensitivity, lack of application to the developing fetus (EPA's decision to not target this potential sensitive subpopulation runs contrary to the SAB direction), assumptions on the nature and impacts of Perchlorate exposure in specific subpopulations, and rates of urinary clearance. EPA does not adequately support these assumptions, further complicating the review by providing contrary uses of existing data, such as from the Greer study (the basis of the National Academy of Sciences report, "Health Implications of Perchlorate Ingestion, 2005). NASA strongly suggests EPA use an open, rigorous peer review of the proposed model to consider and advise on the nature and application of these and other critical assumptions in the formulation of the model.

Again, NASA thanks EPA for the opportunity to review and comment on the proposed Perchlorate model. We strongly request that EPA consider and address the procedural and technical issues identified, especially the strengthening of the rigor and independence of the peer review process, the detailed technical issues raised by partnering DoD and FDA scientists, clarification of the outstanding assumptions and lack of model calibration and validation. We all support sound science in decision making and see these approaches as integral to the formulation of a defensible and applicable Perchlorate model.

Public Comments

Submitted By

Perchlorate Study Group

PSG

PERCHLORATE STUDY GROUP

A coalition of aerospace, defense, chemical and allied industries

October 4, 2016

Via First-Class Mail, Electronic Mail
And Electronic Submission to www.regulations.gov

Mr. Joel Beauvais
Deputy Assistant Administrator
Office of Water
U.S. Environmental Protection Agency
Mail Code 4101
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

RE: Request of the Perchlorate Study Group for an Extension of the Public Comment Period on the "Material to Inform the Safe Drinking Water Act Decision Making on Perchlorate" Docket No. EPA-HQ-OW-2016-0438 [81 Fed. Reg. 67350 (September 30, 2016)]

Dear Assistant Administrator Beauvais:

The Perchlorate Study Group (PSG) hereby requests that EPA extend the public comment period on the draft *Biologically Based Dose-Response (BBDR) Model for Perchlorate* and the accompanying draft model report entitled *Biologically Based Dose-Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Modal Development, Revision, and Preliminary Dose-Response Analyses* for 45 days until December 29, 2016.

A 90-day comment period is the minimum necessary to allow stakeholders an adequate opportunity to understand, evaluate and prepare comments on these materials for the following reasons:

- In 2005 the National Academy of Science recommended that EPA develop a PBPK model for perchlorate in drinking water. EPA elected to not do so until its Science Advisory Board made the same recommendation in 2013. It has taken EPA more than three years since that time to develop the proposed BBDR model. Now, after more than 11 years, EPA is proposing to limit unnecessarily the public's opportunity to analyze and comment on the model. Limiting the comment period to 45 days does not allow for the type of meaningful input from the public that is the essence of notice and comment rulemaking. Providing another 45 days for that review is not unreasonable or unwarranted.

- The Safe Drinking Water Act requires EPA to use the "best available science" when setting a maximum contaminant level. A thorough, objective and unbiased review of the proposed BBDR model by stakeholders is essential to ensuring that the agency has indeed employed the best available science. Such a review cannot be legitimately conducted in 45 days.

- To fully understand and evaluate the extraordinarily complex BBDR model, it is necessary to "deconstruct" it, including identifying and evaluating all of the scientific and policy assumptions embedded in the model. The EPA Perchlorate SAB panel recognized PBPK/PD modeling as "an important and novel opportunity that should be implemented carefully with attention to data quality and methodological rigor." [EPA Perchlorate SAB Report (2013), pp. 3-4.] The SAB panel, clearly acknowledging the complexity of the model and the difficulty to be faced by the public in understanding the model, recommended EPA "develop a clear communications strategy ... [that] will facilitate stakeholder and public understanding of ..." of EPA's approach. (Id. at 19). The SAB panel went on to "emphasize the need for ... transparency and robust explanation of [EPA's] approach and modeling ..." (Id at. 26.) EPA's proposed 45 day comment period does not provide stakeholders with a reasonable opportunity to identify and test the validity of the assumptions EPA has made nor to evaluate whether the model legitimately can predict the effects of perchlorate on human health. As such, it is inconsistent with the SAB recommendations.

- EPA released the model code on two software platforms: AcslV, and "R." The software platform on which BBDR model was developed - AcslV - has been discontinued by the manufacturer and is not available for download. "R" is a free software environment, but several "add-ins" are necessary for a BBDR model to operate on this platform. These add-ins are variations on "R" and require sufficient time and learning to incorporate and develop a working knowledge. EPA's decision to develop the BBDR model on a discontinued software platform is ample reason by itself to extend the public comment period.

The PSG appreciates EPA's willingness to maintain a constructive dialogue with us during the many years that it has been evaluating whether to establish a SDWA standard for perchlorate. We simply ask that the agency be consistent and allow for a reasonable time period for a thorough consideration of the BBDR model.

Thank you.

Sincerely,

Tom Roberts
Van Ness Feldman, LLP
Counsel to the Perchlorate Study Group

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 4/2/2018 3:27:06 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Huff, Lisa [Huff.Lisa@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Status of the Peer Review Report
Attachments: Panel 2 Post-meeting Comment Report_Final.pdf

Hi Eric,

We received the final Peer Review report on Friday. See attached.

Once I get clearance from Lisa I will post to the Docket. We have also drafted an update to the perchlorate website to announce the availability of the report. We also intend to simultaneously send an email blast to the EPA working group as well as to all the attendees to the public meeting announcing the availability.

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Monday, April 02, 2018 11:21 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: Status of the Peer Review Report

Lisa:
What is the status of our peer review report for perchlorate. When do we expect to post it to the web?

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 11/21/2018 10:08:29 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Draft Perchlorate FRN
Attachments: Version-Control Perchlorate Rule FRN 11-21-18 SHQv2.docx

Hi,

I'm sorry, I just realized the earlier message I sent to all of you had an incorrect version of the FRN document.

Please find the correct version attached to this email. My apologies.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Wednesday, November 21, 2018 4:58 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Re: Draft Perchlorate FRN

Thank you Sam. Happy Thanksgiving

Sent from my iPhone

On Nov 21, 2018, at 4:05 PM, Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov> wrote:

> Hi,
>
> Attached you will find the draft Preamble and Regulatory text for the Proposed Perchlorate Rulemaking effort.
>
> Please send your comments and/or edits to me and I will incorporate in the controlled version of the document.
>
> Thank You
> Sam
> ==========
> Samuel Hernández Quiñones, P.E.
> Environmental Engineer
> Office of Water

Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

<Version-Control Perchlorate Rule FRN 11-21-18 SHQ.docx>

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 11/21/2018 9:05:07 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: Draft Perchlorate FRN
Attachments: Version-Control Perchlorate Rule FRN 11-21-18 SHQ.docx

Hi,

Attached you will find the draft Preamble and Regulatory text for the Proposed Perchlorate Rulemaking effort.

Please send your comments and/or edits to me and I will incorporate in the controlled version of the document.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
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"USEPA Protecting Human Health and the Environment"

DRAFT
Pre-Meeting Peer Review Summary Report

External Peer Review for EPA's
Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

January 29, 2018

Peer Reviewers:

Hugh A. Barton, Ph.D.
Nancy Carrasco, M.D., M.S.
Jonathan Chevrier, Ph.D.
Claude Emond, Ph.D.
Dale Hattis, Ph.D.
Angela M. Leung, M.D., M.Sc.
Stephen M. Roberts, Ph.D.
Joanne F. Rovet, Ph.D.

Contract No. EP-C-13-010
Task Order 2015-22

Prepared for:
U.S. Environmental Protection Agency
Office of Ground Water and Drinking Water,
Standards and Risk Management Division,
1200 Pennsylvania Avenue NW (MC 4607M)
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Prepared by:
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Springfield, VA 22151

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I. BACKGROUND

Introduction

EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate. In January 2017, EPA's contractor (Versar, Inc.) conducted an independent, external, scientific peer review of the draft biologically-based dose-response (BBDR; also known as a PBPK/PD) model and report titled *BBDR Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses*. The model predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages and has been revised based on peer reviewer recommendations.

The purpose of this review is to seek guidance from expert peer review on the scientific assessment titled *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (e.g., MCLG Approaches Report) that links the revised perchlorate BBDR model predictions to neurodevelopmental effects to inform decision-making for perchlorate under the Safe Drinking Water Act. The outcome of this peer review is not the derivation of an MCLG; rather, it is to solicit expert comment on the proposed approaches that might be used to inform future decisions on the derivation of an MCLG.

MCLGs are non-enforceable, health-based goals that EPA sets for each regulated drinking water contaminant. In accordance with the Safe Drinking Water Act (SDWA), they are set at a level at which no known or anticipated adverse human health effect occurs and to allow for an adequate margin of safety. MCLGs consider only public health, and not limits of analytical measurement and treatment technology effectiveness. SDWA requires that EPA establish the enforceable Maximum Contaminant Level (MCL) as close as feasible to the MCLG taking costs and benefits into consideration.

Peer Review History

In 2012, as a part of the National Primary Drinking Water Regulation development process for perchlorate and in accordance with the requirements of the SDWA, EPA sought recommendations from EPA's Science Advisory Board (SAB) on approaches to inform the derivation of a perchlorate MCLG.

In 2013, the SAB recommended the following:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling (PBPK);
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode of action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; and
- extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages.

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The SAB stated that this data-driven approach represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages than is possible with the default approach for deriving an MCLG, and that EPA should also consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations. See Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate, EPA-SAB-13-004.

Based on the SAB's recommendations, EPA, with contributions from the Food and Drug Administration, developed a BBDR model to predict the effect of perchlorate on the thyroid gland in formula-fed and breast-fed infants, and in lactating women. This draft model was integrated with a previously published model that similarly predicted the effects of perchlorate on serum thyroid hormone concentrations in the 3rd trimester pregnant woman and her fetus. The model was subjected to external peer review in January 2017. The final peer review report titled *External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water* is available through the docket at https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0439

Revisions to the BBDR Model Following January 2017 Peer Review

EPA considered all of the peer reviewers' recommendations from the January 2017 peer review and focused on those that were anticipated to be most important for increasing the scientific rigor of the model and modeling results. These revisions are summarized in Chapter 3 of the MCLG Approaches Report; additional detail is available in Appendix E. Model revisions focused on the following key recommendations:

- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The revised BBDR model does not explicitly address consideration of other goitrogens. Previous peer reviewers (2017) were mixed on their recommendations regarding the issue of consideration of other goitrogens. A recent review of thiocyanate pharmacokinetics and modes of action indicates that an attempt to address other goitrogens in the model would involve significant uncertainty (Willemin & Lumen, 2017). However, it is expected that the model predictions may, in fact, incorporate the effect of perchlorate along with exposure to other goitrogens because the model predictions for zero perchlorate exposure are calibrated to National Health and Nutrition Examination Survey (NHANES) data, which are from a population with an exposure distribution to other goitrogens that is assumed to be independent of perchlorate.

EPA's Approaches for Informing the Derivation of an MCLG

EPA has developed a two-stage approach linking the revised BBDR model results with quantitative information on neurodevelopmental outcomes from epidemiological studies. EPA has also developed an alternative population-based approach that uses the revised BBDR model to evaluate a shift in the population of pregnant women who could be hypothyroxinemic.

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The first stage of the two-stage approach is the development of the revised BBDR model that describes thyroidal hormone production in women of childbearing age with low/adequate iodide intake and predicts the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. The available data for the second stage of the analysis comes from epidemiological studies that evaluated maternal thyroid hormone levels in early pregnancy and neurodevelopmental outcomes (these are not studies evaluating perchlorate exposure). Based on the recommendations of previous peer review panels, EPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes. For this reason, EPA did not conduct a complete, systematic review of the body of literature on this topic. However, EPA conducted a focused review of the published literature and identified 29 epidemiological studies that examined thyroid hormone levels and neurodevelopmental outcomes. Of these 29 studies, fourteen provide categorical data that assist in understanding the implications of altered thyroid hormones, and fifteen provide more detailed dose-response characterizations via regression analyses to inform the relationship between low thyroid hormone levels and neurodevelopmental effects in offspring.

EPA focused on the latter set of fifteen studies due to their more robust dose-response analyses, which included studies that found statistically significant changes and studies that did not find a statistically significant correlation. Among these studies, the number of subjects ranged from 22 to 3,839. In many of these studies the general outcomes, though not statistically significant showed a positive relationship that was consistent with the studies used for quantitative analyses. In some instances, the studies had results that were negative or inconsistent with the studies that were used for the quantitative analyses. EPA presents and characterizes all of these studies in Chapter 5 of the report.

Five studies in this group of fifteen were identified (Pop et al., 1999; 2003; Finken et al., 2013; Korevaar et al., 2016; and Vermiglio et al., 2004) that included data that were used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy (the focus of the analysis) and changes in neurodevelopment in offspring. Neurodevelopmental outcomes associated with these studies included assessment of Bayley Scales of Infant Development, Weschler Intelligence Scales for Children, a Dutch non-verbal intelligence test (the Snijders-Oomen Niet-Verbale Intelligentie Test) and Standard Deviation of Reaction Time

Using the output from the revised BBDR model (stage 1 of the analysis) and the quantitative relationships between thyroid hormone levels and neurodevelopmental effects from the published epidemiological studies (stage 2 of the analysis), EPA characterized the relationship between perchlorate exposure on fT4 levels in pregnant mothers during early gestation and the potential for changes in neurodevelopmental outcomes in their offspring.

EPA's alternative population-based approach estimates the shift in the population of hypothyroxinemic, pregnant women that would result from perchlorate exposure. EPA used the BBDR model predictions to estimate the proportion of hypothyroxinemic pregnant mothers in the population, assuming a distribution of fT4 levels with a consistent iodide intake.The U.S. EPA's Office of Water is in the process of developing National Primary Drinking Water Regulations for perchlorate under the Safe Drinking Water Act. In 2012, EPA submitted a white paper *Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate* (U.S. EPA, 2012) to the Science

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Advisory Board (SAB) for review. The white paper presented scientific information published since the National Research Council (NRC) released their 2005 Report "Health Implications of Perchlorate Ingestion" and described how EPA derived a range of Maximum Contaminant Level Goal (MCLG) values for life stages of concern. In their 2013 report, the SAB concluded that EPA should: 1) consider exposure to the following sensitive life stages: the fetuses of hypothyroxinemic pregnant women and infants exposed to perchlorate through either water-based formula or the breast milk of lactating women, and 2) derive the MCLG using a physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model to account for exposure differences and biological differences across life stages, including sensitive life stages. Specifically, the SAB found that the 'default algebraic approach provides limited ability to address the various exposure and biological factors affecting sensitivity to perchlorate at different life stages.' The SAB concluded that from a scientific standpoint it would be more appropriate to base the MCLG derivation on the perchlorate mode of action, using PBPK/PD modeling to relate perchlorate concentrations in drinking water to biological effects rather than the default approach.

The SAB report referenced a report by Lumen et al. (2013) on the effect of perchlorate on thyroid hormone perturbations for pregnant mothers and fetuses, as well as their work to extend a physiologically-based pharmacokinetic/pharmacodynamic iodine uptake inhibition (PBPK/PD-IUI) model with links to serum thyroid hormone levels, as a starting point for EPA's efforts.

The new modeling effort presented here integrates the previous EPA PBPK model (2009) for perchlorate with the model developed by Lumen et al. (2013) for pregnant mothers and fetuses (humans) and iodide models developed by Fisher et al. (2013) for lactating rats and Fisher et al. (2016) for lactating mothers and nursing infants (humans). The model has been subjected to a quality assurance (QA) review that was conducted by Oak Ridge National Laboratory (data and parameters used) and Pacific Northwest National Laboratory (model code). The Biologically Based Dose Response (BBDR) model predicts thyroid hormone perturbations for lactating mothers, breast-fed infants and bottle-fed infants resulting from exposure to perchlorate under different dietary iodine intake levels. EPA is relying on the Lumen et al. (2013) model, peer reviewed and published previously, to predict effects for pregnant mothers and fetuses. It is important to note a modification to a key parameter was made (Michaelis-Menten constant for the sodium-iodide symporter for perchlorate, Km) and the thyroid hormone predictions were adjusted for pregnant mothers and fetuses in the model report under review.

EPA is seeking comments on the scientific rigor of the model for evaluating the effects of perchlorate on thyroid hormones in lactating mothers, breast-fed infants and bottle-fed infants under different iodine intake levels. EPA is providing access to the model program code and all necessary files to facilitate use of the BBDR model by peer reviewers and the public. EPA expects that those reviewers with the appropriate software and expertise will be able to replicate the results described in the BBDR model report. After completing development of the BBDR model in the acslX software, the U.S. EPA created a copy of the model that can be run in the alternate software, R. The report URL with links to the code (acslX and R versions for both the pregnancy and infant/lactation models) is:
https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/3352518

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Note that the model is calibrated and expected to be valid for conditions where feedback regulation due to variations in thyroid-stimulating hormone (TSH) levels is minimal, so all charge questions regarding the model are for that range.

In March 2016, the Agency invited the public to nominate scientific experts to be considered as panelists for peer review of the draft model and accompanying report. In June, EPA announced that to achieve efficiency it was expanding the scope of the peer review to include draft approaches for application of the model to inform the development of a perchlorate MCLG. EPA has since reevaluated the review process in response to concerns that a simultaneous review of approaches for application of the model to develop a perchlorate MCLG would not allow for prior consideration of peer reviewer comments specifically on the model.

Therefore, EPA seeks public comment and peer review on the modeling approaches and the ability of the model to predict outcomes that could potentially be used to inform the derivation of an MCLG. EPA intends to seek input on the application of the model for developing approaches for a perchlorate MCLG determination at a later date. Future efforts will include discussion of health endpoints and response levels that are most appropriate to base the MCLG determination.

PEER REVIEWERS

Hugh A. Barton, Ph.D.
Pfizer, Inc.

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UCLA David Geffen School of Medicine

Stephen M. Roberts, Ph.D.
University of Florida

Joanne F. Rovet, Ph.D.
The Hospital for Sick Children (Toronto), Emeritus

DRAFT

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II. CHARGE TO REVIEWERS

Topic #1: General Questions

1. Please comment on the appropriateness of focusing the current evaluation on perchlorate's potential impact on the fetuses of hypothyroxinemic pregnant women during early gestation for the purposes of informing a perchlorate MCLG.

2. Please identify any additional peer-reviewed studies that could inform the BBDR modeling or the quantitative relationship of thyroid hormone levels to neurodevelopmental outcomes. If an alternative study data set would be more appropriate, please outline how such data might be used.

Topic #2: BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy

The revised BBDR model seeks to predict the pharmacokinetics and pharmacodynamics of iodide and perchlorate, as well as the thyroid hormones T3 and T4 and TSH, in non-pregnant and pregnant women, including those with low iodide intake, and changes in thyroid hormone levels.

3. Please comment on the assumptions, strengths and limitations of methods and parameters by trimester for:

    a. determining the quantitative relationships between oral intake and serum levels of perchlorate during pregnancy under continuous exposure assumptions, and

    b. estimating statistical distributions of specific biochemical parameters that determine serum perchlorate concentrations, urine clearance of iodide and perchlorate, and thyroid iodide uptake for purposes of estimating the effect of environmental levels of perchlorate on maternal fT4 concentrations.

4. Please comment on the assumptions, strengths and limitations of the uncertainty analyses of the parameters, particularly with regard to availability of data supporting parameter assumptions.

5. Please comment on the utility of the BBDR model for predicting variability in fT4 levels in the population (e.g., percentiles for different thyroid hormone levels) at varying levels of iodide intake.

6. Please comment on the robustness, precision and sensitivity of the model, and how these factors affect the model's ability to predict changes in fT4 at low perchlorate doses. Consider whether a perchlorate dose range exists for which the modeling predictions would be highly uncertain.

7. The revised BBDR model incorporates a TSH feedback loop defined by an equation from Hadlow et al. (2013) (J Clin Endocrinol Metab, 98(7): 2936-2943), with an adjustment factor

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to match specific data sets or population percentiles, to describe the relationship between fT4 and TSH.

a. Please comment on the assumptions, strengths and limitations of this approach to incorporate a TSH feedback loop into the BBDR model.

b. Noting the reliance on the Hadlow et al. (2013) study, please comment on whether there are other studies that should be considered and describe how they would improve the analysis.

c. Please comment on the approach for characterizing inter-individual variability in relevant populations from which the epidemiological data were obtained.

8. Since the observational thyroid hormone data that are used to calibrate the model derive from populations exposed to goitrogens other than perchlorate, EPA has made an assumption that the model parameters may implicitly account for exposures to these other goitrogens. As such, the exposure to perchlorate is assumed to be effectively added to this background goitrogen exposure as discussed in Chapter 3.5 of the report.

   a. Please comment on the validity of this assumption and the extent of uncertainty associated with this assumption.

Topic #3: Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes

9. EPA conducted a three-step literature review, which identified 15 studies with information that could inform the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes.

   a. Please comment on whether EPA has clearly identified the criteria to identify studies through each of the three steps of the literature review, and the adequacy of the strategy for conducting the literature search. Are these criteria scientifically supportable, and did EPA apply them properly?

   b. Please also comment on the summary and characterization of the literature in Chapter 5 of the MCLG Approaches Report and identify any inaccuracies or mischaracterization of the studies.

10. EPA focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, MDI, PDI and reaction time) based on the measurement of fT4 during early pregnancy at weeks 12, 13 and 16.

    a. Please comment on the assumptions, strengths and limitations of focusing on the five studies and associated neurodevelopmental end points to inform an MCLG, including but not limited to study design, evaluation of neurological endpoints, sample size, iodide nutrition status, potential confounders such as smoking, and study population.

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b. Please comment on whether the chosen studies are sufficient in number, quality, and robustness for the purpose of informing the derivation of an MCLG.

c. Please provide advice on reducing any identified limitations.

11. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

    a. Please comment on the assumptions, strengths, and limitations of using the regression analyses to inform the relationship between thyroid hormone levels and neurodevelopmental outcomes. Please also comment on the various functional forms of the regression equations (e.g. linear, log-linear, quadratic) in each of the relationships.

    b. Please identify additional data or analyses EPA could use to quantify the relationship between thyroid hormone levels and neurodevelopmental effects, including how this information would be expected to improve the analysis.

    c. Please comment on whether there is a magnitude of change in fT4 below which the relationship between fT4 and neurodevelopmental effects should not be used because it is too uncertain.

    d. Please comment on whether other studies that were identified in the literature search (e.g., studies that found categorical relationships between fT4 and neurodevelopmental outcomes, studies that found effects but lacked statistical significance, studies that did not find an effect) could be utilized to quantitatively characterize the relationship between fT4 and neurodevelopmental outcomes or inform uncertainty associated with the analysis presented.

Topic #4: Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes

12. Please comment on the assumptions, strengths and limitations associated with the population-based approach that is focused on a shift in the proportion of the population that could be considered hypothyroxinemic.

13. Hypothyroxinemia is the condition of having an abnormally low level of T4 in the blood and TSH is in the normal range, and in diagnosing this condition the threshold for "abnormally low" is often selected to be the 2.5th, 5th or 10th percentile of the population fT4 distribution. Because the BBDR model can be calibrated to any given percentile, but does not predict the distribution of fT4 levels, it was necessary to derive a fT4 distribution to identify a hypothyroxinemic threshold. EPA assumed a lognormal distribution with a Geometric Standard Deviation based on 2 to 3 studies depending on the gestational week. There is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. For example, some of the analyses show larger unit changes with increasing percentiles of fT4 in most analyses (See tables 24, 30, 31, 32, 33

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and Section 6.5.6 of the MCLG Approaches Report). Please comment on the assumptions, strengths and limitations of the derived fT4 distribution for the purposes of this analysis.

14. Please comment on the strengths and limitations of the two-stage approach versus the alternative population-based approach to inform the derivation of an MCLG.

15. EPA has developed a two-stage approach linking the revised BBDR model results with quantitative information on neurodevelopmental outcomes from epidemiological studies. Please comment on the utility of the this two-stage approach for predicting potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes in the population at varying levels of iodide intake. Please comment on whether there are better strategies for estimating the potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes that are likely to be more scientifically defensible than the approaches presented (e.g. Appendix C estimates IQ impact directly from perchlorate exposure using Steinmaus et al. and Korevaar et al., or potentially some alternative studies). If an alternative approach would be more appropriate, please outline specifically how the approach might be developed given the current available state-of-the-science and data.

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III. GENERAL IMPRESSIONS

Hugh A. Barton, Ph.D.

The draft document and appendices are generally well written and present a sound approach to address the issue of assessing the potential neurodevelopmental impacts of perchlorate exposure during early pregnancy as a sensitive developmental window. The approach is consistent with the recommendations of the 2012-2013 EPA SAB Committee report. That report recommended elaborating the PBPK/PD model to include hormonal changes that would arise in response to perchlorate inhibition of iodide transport, the original endpoint for the model discussed in the 2012-2013 EPA SAB Committee report. It was further recommended that the predicted hormonal changes be linked with dose-response information describing the relationship between altered thyroid hormone concentrations and effects on neurodevelopment.

The current document describes just such an approach, modeling iodine and perchlorate pharmacokinetics, their competitive interaction at the iodide transporter, and the consequences for circulating maternal thyroid hormone concentrations including feedback via TSH and pregnancy induced changes due to hCG. This PBPK/PD model, tested against available information in the literature, is then used to predict impacts of perchlorate on thyroid hormone levels. These levels are then related to expected changes in neurodevelopment based upon published literature describing these outcomes in relation to thyroid hormone levels.

This approach, while it has uncertainties that are described in the report, avoids the major uncertainties of animal to human extrapolation if toxicological studies were proposed as the basis for the MCLG and those noted briefly in a later paragraph from using a simpler approach adjusting the RfD for body weight and drinking water consumption at different life stages. The modeling approach proposed also allows assessment of potential effects of perchlorate in a sensitive window of development during which it would be unethical to carry out a controlled clinical study. This contrasts with the studies of inhibition of iodide uptake evaluated in healthy male and female volunteers, one of the important sources of data for this modeling effort along with epidemiological and observational human studies.

That said, this is a model of substantial complexity due to the pregnancy related changes in iodine and perchlorate pharmacokinetics and in the pharmacodynamics processes regulating thyroid hormone levels. Reading the documents, it is not easy to obtain a clear and thorough understanding of the model's ability to predict median population behavior as well as predict behaviors in the hypothyroxinemic tails of the distribution for pregnant women. Appendix A is much more technically demanding and required expertise in the relevant areas to understand much of the information. Section 1.3, describing the probabilistic analysis, was extremely difficult for this reviewer to read as this was not my area of expertise.

It is worth noting that while public reviewers are appropriately concerned about the uncertainties and potential limitations of this complex modeling approach, the range of potential acceptable drinking water levels (Health Reference Levels) derived using simple body weight and water consumption adjustments for different life stages is reported to be 1 – 47 ug/mL (p 1-4). It is easy to criticize any single approach and difficult to assess the degree of uncertainty across approaches. The simpler default type approach, for example, suggests bottle-fed infants need the

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lowest concentrations while pregnant and non-pregnant women are protected by similar water concentrations because they have similar body weights and drinking water consumption with no consideration of changing iodide needs due to pregnancy. EPA is long overdue in moving forward with public health protections for perchlorate, but may benefit from comparisons among these approaches as it does develop an MCLG.

Nancy Carrasco, M.D., M.S.

Perchlorate contamination of drinking water in the United States is a serious problem because of the deleterious health effects of perchlorate on thyroid physiology. The primary function of the thyroid gland is to biosynthesize and release the thyroid hormones (T_3 and T_4), of which iodine is an essential constituent. The thyroid hormones are master regulators of intermediary metabolism in virtually all tissues throughout life and play a critical role in fetal and early life—specifically, in the development and maturation of the central nervous system, skeletal system, and the lungs. Insufficient amounts of thyroid hormones in the early stages of development lead to mental retardation and stunted growth.

The first step in the biosynthesis of the thyroid hormones is the active transport of iodide (I^-) across the plasma membrane of the thyroid follicular cells. This process is mediated by a specialized plasma membrane transport protein, the Na^+/I^- symporter (NIS), which couples the inward "downhill" translocation of Na^+ down its electrochemical gradient to the inward "uphill" transport of I^- against its *electrochemical gradient.* The central consideration motivating the draft report and the entire effort by the EPA to protect the population from perchlorate contamination is that perchlorate interferes with thyroid function by acting as a competitive inhibitor of NIS, thus preventing I^-, to one or another extent, from reaching the thyroid. Crucially, perchlorate is not only a blocking inhibitor: it is actually a NIS substrate. NIS has a higher affinity for perchlorate than for I^-. It is worth noting that the revised NIS affinity constant for perchlorate reported by Schlosser is exactly the same as that reported by Van Sande *et al.* (2013), a paper that should be cited. Tonacchera *et al.* (2004) reported that the affinity of NIS for perchlorate is 30 times its affinity for iodide. Therefore, in the presence of substantial concentrations of perchlorate in the plasma, NIS will preferentially transport perchlorate rather than I^- into the thyroid, thus decreasing thyroid hormone biosynthesis. In short, NIS is the key molecule at the center of this draft report.

I am a trained physician, a biomedical scientist, and a member of the National Academy of Sciences. My main area of expertise is transport across biological membranes. In 1996, my group was the first to clone the cDNA coding for NIS [Dai et al. (1996) *Nature*], a transporter we have been investigating at the molecular level in great detail for 22 years. We have published over 100 original peer-reviewed articles on NIS and topics related to transport across biological membranes in leading international journals, and have remained at the forefront of NIS research worldwide. We have characterized NIS extensively, elucidated many of its mechanistic and structure/function properties, and intensively studied its regulation and its medical applications, including that NIS is expressed in the lactating breast [Tazebay *et al.* (2000) *Nature Medicine*]. Furthermore, we were the first group to report that NIS actively transports perchlorate, and that it transports it with a stoichiometry (1 sodium : 1 perchlorate) different from the 2 sodiums : 1 anion stoichiometry with which it transports iodide [Dohan et al. (2009) *PNAS*, Paroder-

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Belenitsky *et al.* (2011) *PNAS*]. My impressions, which are informed by these qualifications, are as follows.

Overall, the report was carefully prepared, and it makes significant progress towards the goal of informing the EPA in its effort to derive a maximum contaminant level goal (MCLG) for perchlorate in drinking water. I sincerely commend the authors for what they have accomplished. For example, the report successfully summarizes the available papers on the effect of maternal hypothyroxinemia on the progeny. However, the report, especially in its sections that primarily deal with NIS and the effect of perchlorate on NIS, suffers from the following significant shortcomings: 1. the information presented is sometimes not accurate; 2. the presentation of both concepts and data is sometimes unclear; 3. numerous statements are made without being substantiated by proper references or, sometimes, by any references at all; 4. in many cases, where references are provided, these references are not the most relevant or the most appropriate; and 5. there is a general tendency to use references without regard to their true scientific value; for example, some of the articles cited present conclusions that were reached using outdated techniques that have now been shown to be invalid, and other articles cited are reviews rather than primary research papers, so the actual evidence for the relevant statements is missing altogether. Specific examples of these problems, drawn from throughout the text, are given below (under *III. Specific Observations*). Finally, as a result of these shortcomings, not all the conclusions reached in the report are sound. To give but one example, I am not aware of any evidence of NIS-mediated I^- transport activity in the skin or in erythrocytes, but both of these purported transport processes are nevertheless mentioned in the report as if they had been conclusively established to exist. My impression is that, although the authors of the report made a serious effort to provide evidence from the scientific literature to support their statements, they had no actual longstanding familiarity with the relevant literature on NIS. As a result, several key and seminal original research papers directly germane to the report were not mentioned, while papers with little bearing on the subject at hand or reporting on experiments carried out using outdated or discredited approaches were included.

Jonathan Chevrier, Ph.D.

I commend EPA for engaging in such a complex and ground-breaking enterprise in developing this two-stage BBDR model. The analysis and report were carefully and thoughtfully put together. The idea of using data from physiological parameters combined with epidemiological data in the development of a MCLG is certainly conceptually interesting and would be expected to be of greater value than using the fraction of a no-observed adverse effect level (NOAEL), as is commonly the case. However, this report demonstrates the difficulty of developing such models in a context in which much uncertainty remains. While there is convincing evidence that perchlorate affects circulating fT4 levels and that low fT4 during early pregnancy is associated with impaired neurodevelopment, the parameters underlying these effects are uncertain. Without being an expert in BBDR modeling, my impression was that the model was well thought through and the decisions that were made were well-supported. However, one question remained, which is whether uncertainty in fT4 prediction for each perchlorate exposure level had been quantified. My understanding is that Monte-Carlo types of analyses are generally run on such models to evaluate this uncertainly and I would have expected this to be carried over to the analysis of effects on neurodevelopment but this appeared to be missing. It is also unclear to

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me as to how the model can be validated. This said, my main concern is that the model predicts larger effects among women with higher fT4 levels than those with low fT4. This goes against what would be expected (effects should be stronger at the lower end of fT4), which suggests that issues remain with the BBDR model. My understanding is that this surprising result could be due to the fact that fT4 was assumed to be log-normally distributed. This goes against my own observations and what I have seen in the literature for populations other than first-trimester pregnant women. Although the distribution of fT4 could presumably be different in this population, not all studies reviewed by EPA reported log-normal distributions. In addition, these studies used immunoassays to measure fT4, some of which have been shown to be affected by the concentration of T4-bound proteins. Since the concentration of T4-bound protein changes as pregnancy progresses, fT4 measures from these studies may have been biased. It is unclear to me whether this may explain the skewed distribution of fT4 reported by some studies but this does question unexpected findings. It seems to me that one way or another the BBDR model needs to be adjusted so that its prediction agrees with current knowledge; and it would be useful to see results of the two-stage approach if a normal distribution of fT4 was assumed. Note also that I wonder if the method used to "average" the geometric standard deviations was correct (see comments below). Finally, the lack of usable epidemiologic data that is similar enough that it could be meta-analyzed and the decision to rely solely on studies that generated statistically significant result limit the applicability of the two-stage approach. My overall impression is that the approach has merit but I wonder if the necessary data is available to apply it to this question. I am also unclear as to how the data would ultimately be used to derive a MCLG. This said, I want to make clear that, despite its limitation, I believe that the overall approach has ample merit and is a step in the right direction that ultimately should have a more solid scientific basis than the current approach based on NOAELs derived from animal studies.

Claude Emond, Ph.D.

Here, the goal of this work was to predict the concentration of perchlorate that will induce a significant reduction of the fT4, causing neurodevelopment issue for fetuses during development. Hypothyroxinemia in pregnancy is defined as the presence of a free thyroxine (FT4) value below the 2.5th percentile with the thyrotropin (TSH) level within the reference range. Here, EPA develops a BBDR model trying to relate the exposure of perchlorate to hypothyroxinemia during pregnancy. When we review the document, it is clear to me that several parameters are very variable and not unique. Only trying to understand the relation between TSH and fT4 from the literature is so very different across-study that when plotted on a graph, the conclusion of this relation is difficult to make. It is probably based on the reserves of T4. Other physiologic causes, other than perchlorate, can also be implicated as exacerbating blood fT4 concentration levels in pregnant women. It is important to mention that the quality of the fT4 measurement can also explain the great variability observed in the literature. There is no question for me that the BBDR model is a gold standard for supporting different agencies in their decisions, based on biological plausibility. However, it seems that here, there is the complex harmonization of parameters derived using important statistical energy and fancy approaches. I have no doubt about the mode of action, based on a competition between perchlorate and iodine on the NIS transporters, but I am not sure that we have all the accuracy requested to conduct a risk assessment based on this complex model. The team who worked on this model put in a lot of effort and they are certainly the best in this field to respond to this

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complex question, but I am not convinced that we have a mature model for this task, mostly based on the data available and the complexity of the physiologic change during pregnancy.

Dale Hattis, Ph.D.

Overall EPA has done a creditable job in this analysis. I do have some suggestions for improvement, as outlined in my responses to the charge questions below.

Angela M. Leung, M.D., M.Sc.

The current report provides a complex analysis of the potential effects of low-level environmental perchlorate exposure in women during early pregnancy and their offspring during childhood, and represents an immense amount of work. Compared to the model reviewed in Jan 2017, the incorporation of early pregnancy and the hypothalamic-pituitary-thyroid axis feedback loop into this model is a much more physiologic and relevant assessment of exposure effects in a particularly vulnerable population subgroup and takes into account known compensatory mechanisms resulting from low iodine and/or thyroid hormone levels. In addition, the current model utilizes an exhaustive review of recently published literature (2000-2017) regarding the relationships between maternal hypothyroxinemia during early pregnancy and neurodevelopmental outcomes among their offspring, although only five studies resulting from this search were used for the model.

The current report summarizes an approach based on two stages:

- The first stage summarizes a revised BBDR model, regarding the relationships between iodine status and thyroid hormone production in women of childbearing age, in order to predict the potential effects of maternal perchlorate exposure on maternal thyroid hormone production during early pregnancy.
- In the second stage, the extensive presentation of summaries and key findings of the 15 studies meeting criteria for Group 1 (i.e. studies that evaluated maternal serum FT4 concentrations as a continuous variable during early pregnancy and any variety of offspring neurodevelopment outcomes) offers a detailed look at the most rigorous available studies on this topic at present. These studies were further restricted into the five which had reported a significant adverse effect of neurodevelopmental outcomes in offspring born to hypothyroxinemic pregnant women (thus not studies evaluating perchlorate exposure) to inform the derivation of a perchlorate maximum contaminant level goal (MCLG). The numerous other studies in the literature on this topic were not included as they either reported non-significant findings, did not assess maternal serum FT4 concentrations as a continuous variable, or were not intended to examine offspring neurodevelopmental outcomes.

As none of the five studies in the first approach were based in the U.S. but more importantly, does not provide extensive information regarding maternal iodine status, the report also presents an alternative population-based approach to determine the proportion of pregnant women in a perchlorate-exposed population who would be at risk for having offspring with an adverse neurodevelopment outcome, based on a given steady state of low iodine status.

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Overall, the current report is extensively detailed and generally improved from that discussed in Jan 2017, although the clarity of the writing could still be improved to be relevant for a broader readership, and there remain certain circular redundancies of language that could be addressed to make the report much more concise and overall readable. The charge questions as below were also at times overlapping in nature and leaned more toward model concepts; they may have been better phrased upon consultation with perhaps a more multidisciplinary group of experts.

Although the concepts of the overall model are biologically plausible, I have noted several areas, as below, to potentially strengthen key clinical concepts used to inform the model. My comments are based on my background and perspective as a clinical endocrinologist/thyroidologist with clinical research interests in iodine nutrition, thyroid dysfunction, and thyroid disruptor exposures during pregnancy, post-partum, and early childhood.

Stephen M. Roberts, Ph.D.

There are several important improvements in the BBDR modeling and the accompanying report from the version reviewed in January 2017. Addressing the first trimester fetus as a sensitive life stage, incorporation of a TSH – thyroid hormone feedback loop, extension of the modeling to include quantitative relationships between thyroid hormone effects and neurodevelopmental outcomes, much improved presentation of results and discussion of uncertainties, and overall clarity of presentation are among the most significant changes. The rationale for key decisions is clearly explained and supporting information/data are accurately presented. Overall, the conclusions are sound and the report provides an excellent means to evaluate the scientific strengths and limitations in two proposed approaches to developing a MCLG for perchlorate in drinking water.

Joanne F. Rovet, Ph.D.

Having reviewed the previous draft of BBDR Model Report for Perchlorate in Drinking Water (2016/2017), I find the current version far improved and much clearer in its presentation. In fact, it was a pleasure to read. Furthermore, the current extended version takes into account many of my earlier concerns, particularly: not modelling the HPT axis, not considering the early-in-pregnancy stage, poorly articulated downstream endpoints, use of old references, quality of presentation of results, and poor organization of report itself. Most of these issues have been satisfactorily addressed in what now appears to be a completely overhauled set of processes. The current model is bifold using both former BBDR modeling procedures to extrapolate maternal early gestational free T4 levels from varying perchlorate exposures in a low-iodine environment and using the current epidemiologic literature on offspring outcome following maternal hypothyroxinemia exposure to extract losses in child IQ or alternative endpoints. In the ultimate analysis, potential losses from varying perchlorate levels are individually tabulated according to findings from the five best papers. The writer(s) show an excellent understanding of how to manipulate a massive amount of empirical evidence in order to present cohesive and convincing arguments. This is very impressive.

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However, I still have a number of concerns, particularly the loss of any evidence and specifications for the other critical life stages, namely the later-stage fetus and the breast- versus bottle-fed baby. Granted, large-scale cohort studies of the necessary scenarios for these life stages are not as readily available as they are for those earlier in pregnancy to allow the modelers to derive the necessary numerical information for conducting the second phase of modelling, at least some attempt should have been made to estimate what is happening at these times during development. This is relevant because the brain continues to undergo thyroid hormone-dependent development past the second trimester and for some aspects of cognition and behavior, this latter development has a greater impact on overall life functioning. Note, I don't believe it was ever the intention of the former group of reviewers to remove these life stages.

Despite the excellent quality of presentation of Volume I, I was disappointed in its ending with a lack of summary and take-home message. I thought that some attempt might have been made to better combine the findings of the 5 studies into one set of data (e.g., using standard scores) and to better catalogue in a summary table the findings from remaining Group 1 studies as well as those from the other groups. I did think the author(s) at times got bogged down in the details of the paper. Furthermore, I would have liked the author(s) to discuss the clinical significance of the findings (and maybe even monetary costs); even though the effects were significant, their size was not large.

Notably, too, some critical papers were not discussed, particularly the CATS study findings and the paper by Taylor from this group on perchlorate and the new Pop paper that examines trajectories of maternal hypothyroxinemia throughout pregnancy as a critical factor. Along these lines, I wonder too why the studies measuring maternal TSH primarily were disregarded as this would be at least a marker of maternal thyroid hormone insufficiency to which the fetal brain is exposed. Finally, I found the discussion of thyroid and the brain to be very cursory and based on old literature and I think the author(s) understanding of pregnancy and the fetal compartments is a bit weak.

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IV. RESPONSE TO CHARGE QUESTIONS

Question 1. General Questions: Please comment on the appropriateness of focusing the current evaluation on perchlorate's potential impact on the fetuses of hypothyroxinemic pregnant women during early gestation for the purposes of informing a perchlorate MCLG.

Hugh A. Barton, Ph.D.

The focus on the fetuses of hypothyroxinemic pregnant women during early gestation is completely appropriate and consistent with the recommendations in the US EPA SAB report from 2012-2013. The January 2017 peer review of the PBPK/PD model for end of third trimester and post-natal lactational periods also identified that the literature linking altered thyroid hormone levels with neurodevelopmental impacts was largely limited to consideration of first trimester. Thus, this model addresses the recommendations of that peer review.

Nancy Carrasco, M.D., M.S.

Yes, I agree that it is appropriate to focus on perchlorate's potential impact on the fetuses of hypothyroxinemic pregnant women during early gestation for the purposes of deriving a perchlorate MCLG, because these fetuses are the most vulnerable subjects and the most likely to suffer serious and irreversible intellectual damage if exposed to perchlorate. Therefore, a perchlorate MCLG that protects these fetuses will ensure that other vulnerable populations are also protected.

Jonathan Chevrier, Ph.D.

Fetuses of hypothyroxinemic pregnant women is a population that is likely to be particularly vulnerable to the effect of chemicals on thyroid function. Early gestation, when fetuses cannot produce thyroid hormone and thus depend on thyroid hormone of maternal origin for normal development is also likely to be a sensitive developmental period. Focus on this population and developmental stage is thus highly relevant.

Claude Emond, Ph.D.

The description of the hypothyroxinemic pregnant women is the major issue, as well as the major window of sensitivity. This recommendation was also formulated by the SAB in 2017. I believe it was justified that the EPA requested to do the analysis for the first and second stages of pregnancy as well.

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Dale Hattis, Ph.D.

This seems reasonable; however, the effects of choosing various different degrees of iodide deficiency should be evaluated and reported. I would say that in general that a range for relatively conservative choices of thyroid deficiency should be made, including the 5th, 2nd, 1st, and possibly 0.1 percentiles of the US population, as projected from reasonably representative data for chronic exposures (acute effective one day exposure and/or blood level information from NHANES may need modification to achieve this goal). To do this, studies should be sought of the day to day within-individual variability of blood iodide levels.

Angela M. Leung, M.D., M.Sc.

The current report's focus remains on hypothyroxinemia, similar to the previous report discussed at the Jan 2017 meeting. However, the current report has now shifted to the offspring of women who were hypothyroxinemic during pregnancy, particularly during the first trimester, thus marking a change to an earlier insult, compared from the previous report that was primarily based on hypothyroxinemia during the post-partum period (among lactating women, breastfed infants, and formula-fed infants).

The focus on low maternal serum FT4 concentrations in early pregnancy, rather than another measure such as elevated maternal TSH concentrations, was recommended by the EPA's Science Advisory Board (2013) as the preferred marker of maternal thyroid hormone status in pregnancy. The pros and cons of utilizing hypothyroxinemia as the preferred marker of exposure were summarized at the previous meeting, and these remain the same now. These primarily included the inability to regard hypothyroxinemia in pregnancy as an independent clinical entity, but which has been demonstrated in recent literature to be associated with adverse offspring neurological outcomes.

The shift in the current report to focus on offspring neurodevelopmental measures is appropriate and marks an improvement from the previous report that assessed only serum FT4 concentrations in lactating women and infants. The current understanding of available literature suggests that these outcomes, which may be long-lasting and extend well into adulthood, are the results of low iodine status and/or thyroid hormone levels during mostly early pregnancy.

However, perchlorate exposure is of course not limited to women during early pregnancy. Notably, the lactation sub-model in the previous (Jan 2017) report has been eliminated in the current report. Although the primary focus should be early pregnancy, the early postpartum period represents a still important period of continued neurodevelopment and can be considered a secondary focus of exposure important for lifelong adverse outcomes, including neurocognitive measures. As noted in the Jan 2017 report, there are available data regarding perchlorate content in breastmilk and infant formula, albeit those should also be interpreted with their own limitations as per my previous comments.

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Stephen M. Roberts, Ph.D.

In their 2013 report, the SAB recommended using a PB/PK-PD (BBDR) approach in developing a MCLG for perchlorate in drinking water, and that the EPA include thyroid hormone changes during sensitive life stages for neurodevelopment, specifically mentioning fetuses of hypothyroxinemic pregnant women and infants and neonates exposed to perchlorate through breast milk or water-based formula. The initial BBDR modeling conducted by the EPA, peer-reviewed in January 2017, included these sensitive life stages, although modeling during pregnancy was limited to near term. Comments from the January 2017 peer review meeting strongly recommended that the first trimester of pregnancy be included as a sensitive life stage. The modeling effort currently reviewed is responsive to this recommendation, and in fact focuses on this life stage exclusively. The report explains that the epidemiology supporting a relationship between maternal thyroid hormone levels and neurodevelopmental outcomes is stronger for fT4 in the first trimester than later stages of pregnancy (see page 3-3). In fact, the report states, "This was confirmed by the results of EPA's literature search (summarized in Section 5) which found limited to no data regarding altered thyroid hormone levels and subsequent neurodevelopment effects on life stages other than early pregnancy." (page 1-5). The absence of data to credibly extend the BBDR modeling to neurodevelopmental outcomes for other life stages makes the decision to focus on early pregnancy appropriate in my opinion. However, it leaves unresolved the status of the other sensitive life stages — specifically, infants and neonates exposed through breast milk or water-based formula. Are they assumed to be less sensitive, and thus protected by a MCLG developed based on the first trimester fetus? If so, what information is available to support that assumption? Or is there simply not enough data to indicate the comparative sensitivity of the other life stages? If that is the case, it creates an uncertainty in MCLG development that merits additional discussion.

Joanne F. Rovet, Ph.D.

It is important that this period of development is examined, but not to the exclusion of the other sensitive periods. It is really a matter of convenience as the bulk of the cohort studies obtained maternal data at these times. I would have liked a better justification of why this period (and this period alone) is so critical. Bernal has recently shown that cerebral cortex neurogenesis takes place during this window. Perhaps some emphasis on this would rationalize this focus. However, the author(s) must be clear that further critical aspects of brain development are occurring in later windows and they are thyroid-hormone dependent. Perhaps incorporate some of the congenital hypothyroidism findings and some of the newborn screening (normal) results, especially if these were used as controls in neurodevelopmental studies. Perhaps too, include summarized findings of the studies on transient hypothyroxinemia of prematurity including those by this reviewer. This work covers the late-in-pregnancy sensitive period.

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Question 2. General Questions. Please identify any additional peer-reviewed studies that could inform the BBDR modeling or the quantitative relationship of thyroid hormone levels to neurodevelopmental outcomes. If an alternative study data set would be more appropriate, please outline how such data might be used.

Hugh A. Barton, Ph.D.

Not aware of any additional studies.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

I am not aware of studies other than those used or otherwise mentioned in this report.

Claude Emond, Ph.D.

I did not find any additional peer-reviewed studies that would add significant information to challenge this work.

Dale Hattis, Ph.D.

I didn't come across any.

Angela M. Leung, M.D., M.Sc.

For the current report, a comprehensive search was performed of published studies regarding the relationships of serum thyroid hormone concentrations and neurodevelopmental outcomes. However, the search was restricted to studies published in 2000 and later. This approach omits the important study by Haddow et al. (NEJM, 1999; PMID: 10451459), which in fact did measure maternal serum TSH, TT4, and FT4 concentrations (erroneously stated in the current report that serum TT4 and FT4 were not measured) and correlated to their offsprings' neuropsychological test scores at ages 7-9. This was one of the first reports to demonstrate an adverse effect of maternal hypothyroidism during pregnancy on childhood neurocognitive outcomes, is considered a seminal article regarding this topic, and should be included.

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Stephen M. Roberts, Ph.D.

I am not aware of any additional peer-reviewed studies that would be useful for the BBDR modeling or in establishing a quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes.

Joanne F. Rovet, Ph.D.

Taylor PN et al JCEM 2014 99:4291-4298 (cited but not properly discussed)
Bath SC et al Lancet 2013 382:331-337
Lazarus JH et al NEJM 2012 366: 493-501 and later studies now in publication
Bernal J, J of Endocrinology 2017 232: R83-R97
Bárez-López S et al, Cerebral Cortex 2017 Apr 12 1-11
Pop et al 2017 Longitudinal trajectories … in thyroid function - ?different from Endendijt paper
Casey BM &Thom EA NEJM 2017 377: 701
Casey BM et al 2017 376: 815-825

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Question 3. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy</u>. Please comment on the assumptions, strengths and limitations of methods and parameters by trimester for:

Question 3A. Determing the quantitative relationships between oral intake and serum levels of perchlorate during pregnancy under continuous exposure assumptions, and

Hugh A. Barton, Ph.D.

Model simulations compare well with data for non-pregnant women (Section 2.1 in Appendix A) and males. Adjustments of physiological parameters are made for pregnancy, so in the absence of other data, it is appropriate to assume that the model reasonably predicts perchlorate pharmacokinetics during pregnancy.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

The method for determining the relation between oral intake and serum levels of perchlorate appeared appropriate to me. BBDR modeling being outside of my area of expertise, I do not feel that I can comment further on the assumptions, strengths, and limitations of the method and parameters.

Claude Emond, Ph.D.

It is reported in the document that "Several short-term (two-week exposure duration) studies have reported that exposures ….. decreases in iodide uptake, <u>but not with changes in levels of thyroid hormones in the blood"</u> (V1, page 1-2, p15) This is because the reserve of T4 is relatively high. What would the dose that will really impact the homeostasis and spent the dose causing a hypothyroxinemia?

Dale Hattis, Ph.D.

The relationship between external exposures to perchlorate and serum levels of thyroid hormones in the current EPA analysis appears to be primarily inferred from a recent paper of Steinmaus et al. (2016). This is a good paper based on extensive relevant observations of the association between serum thyroid hormone levels and urinary perchlorate observations (the latter, a good indicator of recent exposure to perchlorate).

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Unfortunately, the Steinmaus analysis choses to use a log-transform of the urinary perchlorate in its regressions, e.g., serum thyroid hormone concentration in the blood (that is, total T4, fT4, and the related variable TSH) = Log10(urine perchlorate) + other regression variables.

My past experience is that there are few, if any, biological mechanisms that lead naturally to an expectation of a log-linear dose response relationship. Instead, mechanistically based Michaelis-Menten enzyme kinetics leads more naturally to another mathematical form:

Effect = Emax*[C]/(Km + [C]

Where [C] is the substrate concentration (i.e., perchlorate in this case), Emax (change in thyroid hormone concentrations) is the maximum effect that can be produced at the the limit of high [C], and Km is a constant

For convenience in regression analysis, the Log(10)[C] in the Steinmaus et al. (2016) regression analyses could be replaced by:

[C]/(Km + [C]),

where an optimal value of Km for the regression can be found, by trial and error, using multiple runs of the regression with different candidate values of Km. This optimality can be judged by maximizing the R squared statistic.

Log transformations of both dependent and independent variables have a long and hallowed tradition in analysis of epidemiological data. However, while there can be some statistical benefit in normalizing a dependent variable by log transformation, this does not carry forward to the domain of independent variables. There can be no general expectation for no improvement in the properties or accuracy of regression analysis from making the distribution of an independent variable closer to normal. Instead, the analyst will improve the description of the real causal relationship most by having the fitted equation resemble as closely as possible the real causal relationship that gave rise to the observations.

Angela M. Leung, M.D., M.Sc.

The perchlorate sub-model in Figure 4 of the main report, as well as Section 1.2 of Appendix A, were reviewed. Appendix A states that perchlorate ingestion is not metabolized, thus is assumed to be 100% absorbed and equal to the steady state delivery to plasma. Available literature appears to support this and demonstrates that perchlorate is excreted intact in the urine with 95% recovery within 72 hours (Soldin et al, PMID 11477312). Given this, the assumption that nearly 100% of ingested perchlorate will circulate in plasma unchanged appears to be appropriate.

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Stephen M. Roberts, Ph.D.

The perchlorate sub-model treats perchlorate as being delivered directly to the central compartment (no transformation in the GI tract and 100% absorption). This simplification could affect simulation of short-term perchlorate kinetics, but is less of an issue for longer-term model predictions most relevant to the BBDR modeling. Modeling has been strengthened by the addition of a number of refinements, including protein binding of perchlorate in blood and distribution into red blood cells. One limitation in modeling perchlorate kinetics in pregnancy is the absence of suitable kinetic data from pregnant women. As a result, data from non-pregnant women and men had to be used for comparison with model predictions. Changes in the clearance rate of perchlorate during pregnancy were estimated from an empirical relationship between gestational age and glomerular filtration, and the relationship between glomerular filtration rate and iodine clearance. These approaches to the absence of PK data from pregnant women are reasonable but contribute to uncertainty in perchlorate blood concentration predictions.

Joanne F. Rovet, Ph.D.

While Figure 4 seems reasonable to me from the point of view of the mother, it does not account for the fetus and for the fetal brain, which ultimately need their thyroid hormone. There is no accounting for the different sacs and how perchlorate may interfere with thyroid iodide to the fetus via the coelomic sac (earliest pregnancy) and amniotic sac (later). Similarly, there is no system that models thyroid hormone from the mother to the fetal brain and into the brain via the blood-brain barrier (to cortex) and choroid plexus (to subcortical regions and posterior cortex). It is said that NIS receptors are found in the choroid plexus, so what happens if these are blocked?

DRAFT

ED_005043_00063236-00026

Question 3. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy</u>. Please comment on the assumptions, strengths and limitations of methods and parameters by trimester for:

Question 3B. Estimating statistical distributions of specific biochemical parameters that determine serum perchlorate concentrations, urine clearance of iodide and perchlorate, and thyroid iodide uptake for purposes of estimating the effect of environmental levels of perchlorate on maternal fT4 concentrations.

Hugh A. Barton, Ph.D.

Estimation of statistical distribution is not this reviewer's area of expertise. It was not entirely clear how the use of some parameters as a specified lower percentile, e.g., CLFUP as 2.5th percentile value, fit together with the distributional aspects.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

The methods used to estimate the distribution of parameters that determine serum perchlorate concentrations, urine clearance of iodide and perchlorate, and thyroid iodide uptake appear adequate. Again, BBDR modeling being outside of my area of expertise, I do not feel that I can comment further on the assumptions, strengths, and limitations of the method and parameters. However, I note that it appears that the literature was searched systematically for published data necessary to identify the distribution of parameters and the relation between variables. Whenever possible, raw data was requested to perform additional analyses. It is apparent that decisions were made after careful evaluation.

Claude Emond, Ph.D.

This is a very sophisticated approach, using all those statistics, but in the end, I am not sure about the improvement (advancement) of these sophisticated approach. I hope we will have an explanation during the meeting.

Dale Hattis, Ph.D.

See comment to Question 3A.

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Angela M. Leung, M.D., M.Sc.

I reviewed the values summarized in Table 1, but this is not my area of expertise and cannot comment further.

Stephen M. Roberts, Ph.D.

Variability in maternal fT4 concentrations was estimated based upon studies with fT4 data from 12, 13, and 16 weeks of gestation. Although the number of available studies was small (3), the use of variability data from human subjects is an important strength. Data were assumed to be lognormally distributed, and a geometric standard deviation (GSD) was used to quantify variability. As the report points out (page 4-6), although the data were right-skewed, a distribution other than lognormal may better describe the variation in fT4. Time and resources permitting, it would be useful to explore other distributions, as the population variability in fT4 is important in predicting perchlorate effects at various percentiles.

Joanne F. Rovet, Ph.D.

This is beyond my competence.

DRAFT

ED_005043_00063236-00028

Question 4. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy</u>. Please comment on the assumptions, strengths and limitations of the uncertainty analyses of the parameters, particularly with regard to availability of data supporting parameter assumptions.

Hugh A. Barton, Ph.D.

No comment.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

I do not feel qualified to answer questions 4-7 and prefer not to comment.

Claude Emond, Ph.D.

The strategy used to consider the uncertainty and the variability was correctly applied. They analyzed all the parameters as mentioned on page A-97 (103 in pdf). The outcome was the variation of the fT4. Here they reported only parameters with relative change higher than 0.1, which is fine.

Dale Hattis, Ph.D.

The document has a quite extensive qualitative discussion of the uncertainties of the analysis. It could be improved by drawing some quantitative inferences about how large the uncertainties from different sources are likely to be.

Angela M. Leung, M.D., M.Sc.

The report described several uncertainties in Section 3.5:

- **Placental and fetal iodine and thyroid hormone content**: Page 43 of the report states that the absolute contribution of iodine and thyroid hormone stores in the placenta and fetus toward those in the mother are likely insignificant, thus there are not separate placental and fetal sub-models. I agree that this is likely appropriate, since the fetal thyroid does not begin to develop structurally until approximately 10-12 weeks of

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gestation, and remains very small in size (relative to the maternal thyroid) with likely very little iodine and thyroid hormone content throughout gestation.

- **Iron deficiency**: Page 43 describes the potential impact of iron deficiency on hypothyroxinemia as an uncertainty. Although iron deficiency anemia is the most common cause of anemia during pregnancy, we do not seem to observe hypothyroxinemia commonly in the clinical setting among women with iron deficiency. I would agree that maternal iron deficiency is unlikely to be a significant contributor for the purposes of the model and does not have to be accounted for. Of note, the 2016 ATA pregnancy guidelines also do not mention iron deficiency.
- **Coexposures**: Page 45 states the potential uncertainties of the model resulting from coexposures to other environmental and dietary thyroid disruptors. Accounting for wide number of these unmeasured substances is impossible, and thus it is appropriate to leave this issue as a limitation of any exposure model, as was stated in the report to be present also in the NHANES datasets. One consideration, however, is thiocyanate as the one exposure with sufficient available data to likely further improve the perchlorate model (see my comments to Question #8).
- **Competitive effect at low perchlorate concentrations**: Page 45 describes the uncertainty of the model based on the effect perchlorate on iodine uptake as mediated by NIS at low perchlorate levels. It is appropriately stated that current understanding demonstrates no additional magnification of this effect even at lower perchlorate concentrations.
- **Potentiation of other thyroid disease**: Page 46 lastly describes the potential uncertainty of environmental perchlorate exposure on potentiating the development of other thyroid diseases, such as Hashimoto's thyroiditis. Although this is certainly possible, current understanding is limited to lacking on this topic, thus it is appropriate to leave this as an uncertainty of the model.

Stephen M. Roberts, Ph.D.

A semi-quantitative analysis of uncertainty and variability of the parameters was conducted through a Local Sensitivity Analysis presented in Appendix A. Although ranges of values were not determined in a statistically rigorous way, the analysis nevertheless provides a rough estimate of the range of potential values compared with the central estimate. This analysis is adequate for the purposes of the report.

Joanne F. Rovet, Ph.D.

I am not too sure if the TSH feedback loop is properly incorporated and how, but I may be wrong. Note the Hadlow paper shows sex and age differences. Were these values incorporated into the model. Are the various transporters incorporated into the model?
Are individual differences in sensitivity of TSH incorporated into the model, as mentioned on page 3-9. What about the assumption (mine) that continued exposure to low iodine and perchlorate may put the hyothalamus and pituitary into overdrive and create a form of resistance, perhaps leading to later hypothyroidism, which can happen during pregnancy when the system is

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stressed. Is this being accounted for in the model? Interestingly, these cases were eliminated in the second part of the analysis.

I am not too sure what is meant by the statement "Increased urinary clearance of both iodide and perchlorate during pregnancy (why?), described by the model, have the conflicting effect of both reducing … so these two components of pregnancy-related changes will cancel each other out to some extent".

DRAFT

ED_005043_00063236-00031

Question 5. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy</u>. Please comment on the utility of the BBDR model for predicting variability in fT4 levels in the population (e.g., percentiles for different thyroid hormone levels) at varying levels of iodide intake.

Hugh A. Barton, Ph.D.

Since changes in fT4 levels are a key output of the model, its ability to predict them for varying levels of iodide intake is important.

The comments submitted by American Water Works Association (AWWA), based upon a review by Gentry et al., states that these levels are not adequately predicted. In response to this concern, I undertook some review of the modeled median fT4 levels during pregnancy without perchlorate exposure. It is difficult to understand what is going on with different values ranging from about 10-15 pmol/L in different figures and tables at gestation weeks 12 – 16 (e.g., Fig A-57 14-15 pM; Table 2 10-11 pM for 170 ug/day iodide; Fig 5 ~10.5 pM). Since Fig A-57 represents data from studies and appears well simulated, it is not clear what is different in Table 2 and Fig 5.

Gentry et al. ran the model to compare results with three studies, and presumably their findings contributed to their comments that the model did not adequately predict. The problem for both the Steinmaus et al. 2016 study and the highest dose of Greer et al. 2002, was that the model under predicted the extent of perchlorate-mediated changes, while for Tellez Tellez et al. 2005 predictions were consistent. Thus, it isn't clear that the model inadequately predicts, or if it does, it appears to be insufficiently responsive to perchlorate-mediated effects.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

I do not feel qualified to answer questions 4-7 and prefer not to comment.

Claude Emond, Ph.D.

I am not convinced at this stage of the relevance, usefulness, and resilience of this model to predict the influence of perchlorate to significantly reduce the concentration of fT4 in pregnant women.

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Dale Hattis, Ph.D.

See detailed comments on the variability analysis in my response to question 7 below. A priori I have no difficulty with the use of the model as now done in the document.

Angela M. Leung, M.D., M.Sc.

The model's incorporation of other factors, such as the TSH feedback loop and effect of bHCG, strengthens the ability to predict maternal serum FT4 levels, at varying levels of iodine intake. The model's estimation of dietary iodine intake is summarized in Appendix Section 2.2.1, which is based on a spot urinary iodine concentration collected from NHANES participants and adjusted for known or estimated daily urine volumes.

However, there can be substantial diurnal and day-to-day variations in urinary iodine concentrations in a given individual (Rasmussen et al, PMID 10359497). Given this, it is not surprising that the current report found no relationship between dietary iodine estimates and serum FT4 concentrations in the NHANES datasets. The accuracy of the iodine intake values is a limitation to the model predicting serum FT4 concentrations. Overall, the challenge is that individual iodine status is difficult/impossible to estimate; only population iodine status can more reliably be determined.

The present report can also consider the points made in the following article by Brucker-Davis and colleagues demonstrating no effect of iodine supplementation in later pregnancy (albeit later pregnancy) on serum FT4 concentrations (PMID 24847452), which was reviewed briefly for *Clinical Thyroidology* and *Clinical Thyroidology for the Public* as below:

https://www.thyroid.org/patient-thyroid-information/ct-for-patients/vol-6-issue-12/vol-6-issue-12-p-4-5/.

https://www.thyroid.org/wp-content/uploads/publications/clinthy/clinthy_v2510.pdf

Stephen M. Roberts, Ph.D.

As indicated in Figure A-57, the BBDR model predicts variability in fT4 levels as a function of iodide uptake reasonably well.

Joanne F. Rovet, Ph.D.

It seems reasonable, although I still had difficulty reading the simulation graphs (p3-11).

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Question 6. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy</u>. Please comment on the robustness, precision and sensitivity of the model, and how these factors affect the model's ability to predict changes in fT4 at low perchlorate doses. Consider whether a perchlorate dose range exists for which the modeling predictions would be highly uncertain.

Hugh A. Barton, Ph.D.

EPA provides a wide range of information on fits to different data sets and sensitivity analyses. Not surprisingly, the model fits some data better than others, but it is not obvious that there is a consistent problem in a specific area of biology or dose range. Gentry et al., in their comments for AWWA, question whether the model should be relied upon for small changes in model outputs (e.g., <1%), such as fT4. Given the variability in existing data and the complexity of the decisions involved in putting together this model, it does seem reasonable to be concerned that very small predicted changes in model outputs might be more difficult to characterize for how well supported they are compared to somewhat larger change (e.g. >1-2%).

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

I do not feel qualified to answer questions 4-7 and prefer not to comment.

Claude Emond, Ph.D.

My impression is that several parameters have been adjusted and statistically optimized because of missing measured parameters. However, even though we performed this optimization, we can see that the relation between TSH and fT4 are still compared to a cloud of data points from biomonitoring. The figures (Fig 5Vol 1, page 3-11; figure A-44 A-46 Vol2 page A-70), precise that the simulation of TSH showed that an increase of perchlorate exposure result in a decrease of fT4 resulting in an increase of TSH. Nevertheless, we can see that the model simulation curve is in the middle of a cloud obtained by biomonitoring of a dataset. Meanwhile, I am still thinking about what I observe if it is the best curve corresponding to the biological relevant or the reality is more variable and how confident I am with this prediction. The model is usable to determine the Maximum contaminant level goal (MCLG). However, more data need to be generated to improve the confidence of the predictability for this model.

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Dale Hattis, Ph.D.

I have no problem with the current treatment of this issue in the document. There is some reason for concern however about the accuracy of the current model at very low levels of iodide intake where the induction of TSH may or may not be accurately represented by the current model. There will clearly be some chronic reduction in internal stores of iodide and the response of the system under those conditions has not been clearly tested. However, low perchlorate dose levels do not, in my opinion, give rise to similar concerns.

Angela M. Leung, M.D., M.Sc.

- **Dietary iodine**: Comments as above in question #5.
- **Iodine intake in non-pregnant vs. pregnant women**: The results shown in Section 3.4 and Figure 5 show example outputs from the BBDR model of non-pregnant individuals and pregnant women. It is unclear to me whether the model takes into account the increased iodine need in pregnancy (extra 70 mcg/day), compared to non-pregnant adults (see Table 1 in Leung et al, PMID 22108279), that U.S. pregnant women are advised to be (albeit not uniformly) receiving (Alexander et al, PMID 28056690). Section 3.3 does state that the model adjusts for the increased serum T4 concentrations in pregnancy, for which the increased iodine need is one reason underlying this.
- I defer to the other reviewers regarding the remainder of the model.

Stephen M. Roberts, Ph.D.

As the report points out, data in humans with which to compare BBDR model predictions for perchlorate effects on fT4 are very limited. Appendix B shows a comparison of BBDR model predictions with fT4 data and perchlorate exposure from Steinmaus et al. Those comparisons show some difference in the closeness of the model prediction with Steinmaus et al. data with perchlorate dose, but overall the model appears to under-predict, substantially, changes in fT4 with perchlorate dose. There are some important limitations in this comparison due to limitations in the Steinmaus et al. study, including lack of concurrency in perchlorate exposure estimation and fT4 measurements.

Joanne F. Rovet, Ph.D.

One concern I had throughout the report is why perchlorate dose increases by 1 unit until 5 micrograms/kilo/day and then jumps to 10. Why?

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Question 7. BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy. The revised BBDR model incorporates a TSH feedback loop defined by an equation from Hadlow et al. (2013) (J Clin Endocrinol Metab, 98(7): 2936-2943), with an adjustment factor to match specific data sets or population percentiles, to describe the relationship between fT4 and TSH.

Question 7A. Please comment on the assumptions, strengths and limitations of this approach to incorporate a TSH feedback loop into the BBDR model.

Hugh A. Barton, Ph.D.

Appeared reasonable.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

I do not feel qualified to answer questions 4-7 and prefer not to comment.

Claude Emond, Ph.D.

Because TSH is a hormone, responsible for retro feedback, the production of T4 is essential in the BBDR model. The problem seems to be more the quality of the data showing an important variability make difficult to get a better accuracy of the. It also seems that threshold certainly seems implicated induced the reserved of T4.

Dale Hattis, Ph.D.

I agree that the interindividual variability distribution for fT4 should be presumed to be lognormal. However, the approach for combining estimates of variability from different datasets shown in Table 5 (p. 49) is not correct. Geometric standard deviations should never be simply averaged. Variances (the squares of the standard deviations) should be used as the basis for calculating weighted averages. In this case, because the GSD estimates from different data sets refer to lognormal distributions, the variances represent the variances of the distributions of the logarithms of the fT4 levels.

Delving into the detailed numbers provided in Table 5 requires some interpretation. Because the numbers in the second and third columns of the table are all less than 1, they cannot represent GSDs. My best guess is that they represent standard deviations of the logarithms of the

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underlying distributions of fT4 levels. Corresponding GSDs would have to be the anti-logs of these values, e.g. $10^{\text{table values in Columns 2-3}}$. Given this assumption/guess, Table A on the next page gives my inferences for combined log(GSDs) for the different cells in Table 5. (Results are expressed to many more significant figures than are warranted to allow precise replication of the calculations. The accompanying Excel spreadsheet shows the numerical derivation of these estimates.

It can be seen in the results in Table A that, as it happens, there are very small differences between these results of this corrected combination of lognormal distributions from the results provided in the initial Table 5 given in the document. Nevertheless, I believe it is important to correct the methodology and presentation of results and to revise the subsequent table based on the altered table 5 because EPA will not wish to provide a basis for later technical challenge to the policy-relevant risk estimates that will eventually be derived.

Table A
Recalculated Values for Table 5 Based on Combining Lognormal Variances Rather than GSDs

	Log Variance from 2.5th percentile estimate	Log Variance from 97.5th percentile estimate	Combined	Calc log(GSD) from 2.5th percentile estimates	Calc log(GSD) from 97.5th percentile estimates	Combined estimate of log(GSD)
	0.024320403	0.02286144	0.023590921			
	0.019912032	0.028224	0.024068016			
	0.015592517	0.032634423	0.02411347			
	0.013384176	0.011487552	0.012435864			
Weighted average variance	0.01847841	0.027524703	0.023001556	0.135935315	0.165905704	0.15166264
	0.02042041	0.02515396	0.022787185			
	0.01687401	0.008918914	0.012896462			
Weighted average variance	0.01888243	0.018113251	0.018497841	0.137413356	0.134585479	0.136006767

Angela M. Leung, M.D., M.Sc.

It is appropriate for the revised model to include considerations of the hypothalamic-pituitary-thyroid feedback loop, in which serum TSH concentrations will be simulated based on predicted serum FT4 concentrations, for use in the feedback loops shown in Figure 4, specifically the action of TSH on thyroidal NIS.

However, the following assumptions should be further clarified: 1) the stimulatory action of TSH on NIS should also be in the perchlorate sub-model, since it is the same NIS in both the perchlorate and iodide sub-models; 2) the inhibition of perchlorate on NIS in the iodide sub-model should be technically from the perchlorate content in thyroid plasma, rather than NIS, in the perchlorate sub-model.

It should also be noted that there is some variation in the TSH feedback mechanism amongst individuals (i.e. there are likely not a discrete FT4 setpoint at which increased TSH is universally triggered).

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Stephen M. Roberts, Ph.D.

I have not yet formed an opinion on this question and look forward to discussion with other panel members during the face-to-face meeting in formulating my response.

Joanne F. Rovet, Ph.D.

This seems reasonable as this looks to be a good study.

DRAFT

ED_005043_00063236-00038

Question 7. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy.</u> The revised BBDR model incorporates a TSH feedback loop defined by an equation from Hadlow et al. (2013) (J Clin Endocrinol Metab, 98(7): 2936-2943), with an adjustment factor to match specific data sets or population percentiles, to describe the relationship between fT4 and TSH.

Question 7B. Noting the reliance on the Hadlow et al. (2013) study, please comment on whether there are other studies that should be considered and describe how they would improve the analysis.

Hugh A. Barton, Ph.D.

No comment.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

I do not feel qualified to answer questions 4-7 and prefer not to comment.

Claude Emond, Ph.D.

I am not aware of any other publication that might improve the analysis. However, if we look at Figure A-46, there is so much variability between studies that I am not sure about the plus value of this statistic. There seems to be a large uncertainty in this relationship. However, using only Hadlow is not enough, even if there are "data from over 150 thousand subjects". The correction added in the equation seem interesting, but using that we increase the uncertainty of the Hadlow equation.

Dale Hattis, Ph.D.

See comment to Question 7A.

Angela M. Leung, M.D., M.Sc.

The classic log-linear relationship between serum TSH and FT4 concentrations has long been recognized, which the Hadlow et al. article used to define this feedback loop in the current model does not support. The report does not sufficiently describe the reasons why this equation comprised of two sigmoidal curves was chosen to model the relationship between TSH and FT4.

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A commentary of the Hadlow article by Dr. Elizabeth Pearce was published in *Clinical Thyroidology* (https://www.thyroid.org/professionals/ata-publications/clinical-thyroidology/july-2013-volume-25-issue-7/clin-thyroidol-201325156-157/), which summarizes the strengths and limitations of this paper, as well as citations of three other papers (references 1-2) which can also be considered.

Stephen M. Roberts, Ph.D.

I am not aware of other studies that should be considered to improve the analysis.

Joanne F. Rovet, Ph.D.

Perhaps check out the CATS data.

DRAFT

ED_005043_00063236-00040

Question 7. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy.</u> The revised BBDR model incorporates a TSH feedback loop defined by an equation from Hadlow et al. (2013) (J Clin Endocrinol Metab, 98(7): 2936-2943), with an adjustment factor to match specific data sets or population percentiles, to describe the relationship between fT4 and TSH.

Question 7C. Please comment on the approach for characterizing inter-individual variability in relevant populations from which the epidemiological data were obtained.

Hugh A. Barton, Ph.D.

No comment.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

I do not feel qualified to answer questions 4-7 and prefer not to comment.

Claude Emond, Ph.D.

The variability is certainly the major influence affecting the level of confidence of the PBPK model. The improvement of the analytical method used in the identification of TSH, fT4, and total T4 should be included in the recommendation.

Dale Hattis, Ph.D.

See comment to Question 7A.

Angela M. Leung, M.D., M.Sc.

The report acknowledges several areas of potential inter-individual variability:

- **NIS**: It is reasonable to state that the degree of potential variation in NIS structure and/or regulation across individuals is unknown.
- **TSH response**: It is reasonable to state that there may be inter-individual variability in the magnitude of a TSH response following perchlorate exposure, due to the stated differences in genetics, subclinical thyroid dysfunction, age, gender, cigarette smoking, coexposures, and likely other factors. The acknowledgement that these are likely

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contributors, but which remain unable to be further built into the present model, is sufficient.

- There are also nonmeasured factors such as genetics and coexposures that may be important. Any variability in the above factors and others is best minimized with large epidemiologic datasets. Unless otherwise noted, it is a reasonable assumption that the datasets used to build the current model are appropriate.

Stephen M. Roberts, Ph.D.

I have not yet formed an opinion on this question and look forward to discussion with other panel members during the face-to-face meeting in formulating my response.

Joanne F. Rovet, Ph.D.

This represents a definite improvement in the approach. The authors have been very thorough and systematic. Their work here represents one of the best compilations of the field.

DRAFT

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Question 8. <u>BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy.</u> Since the observational thyroid hormone data that are used to calibrate the model derive from populations exposed to goitrogens other than perchlorate, EPA has made an assumption that the model parameters may implicitly account for exposures to these other goitrogens. As such, the exposure to perchlorate is assumed to be effectively added to this background goitrogen exposure as discussed in Chapter 3.5 of the report.

Question 8A. Please comment on the validity of this assumption and the extent of uncertainty associated with this assumption.

Hugh A. Barton, Ph.D.

This assumption appears reasonable because the responses observed in the human population reflect the full range of causes of population variability, e.g., genetics, life stage, co-exposures to goitrogens, and variations in iodide intake. While intellectually it would be interesting to understand the interplay among all these factors, it does not appear necessary for current purposes. For the responses to perchlorate to be substantially incorrectly attributed to perchlorate, it would have to be the case that the levels of perchlorate exposure were very highly correlated with exposures to other goitrogens.

Nancy Carrasco, M.D., M.S.

The topic of BBDR modeling and the fields of pharmacokinetics and pharmacodynamics are outside my area of expertise; I am therefore unable to comment on this topic.

Jonathan Chevrier, Ph.D.

This may be the case if one assumes that samples used in studies used to generate the data were representative of the U.S. population. This means that the distribution of all factors that could modify the relations between exposure to perchlorate and fT4/neurodevelopment should be similar in study samples as it is in the general U.S. population. Given the fact that most studies did not have a probabilistic sampling design, that most used non-U.S. population that may have different exposures to goitrogens, and considering the modest sample size of most studies used in this report, EPA's assumption is likely to be over-optimistic. EPA may want to consider applying a safety factor to derive the MCLG to account for exposure to other goitrogens.

Claude Emond, Ph.D.

No comment at this time.

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Dale Hattis, Ph.D.

This seems to me to be a reasonable assumption.

Angela M. Leung, M.D., M.Sc.

Please see my comments regarding exposures to other thyroid disruptors in Question #4. The assumption that the datasets used to calibrate the model also contained exposures of unaccounted substances is reasonable.

Specifically, however, thiocyanate is the one goitrogen that may deserve further consideration for incorporation into the model. Thiocyanate is a byproduct of cigarette smoke and present naturally in certain *Brassica* vegetables, thus is a potentially common and ubiquitous exposure. Like perchlorate, thiocyanate inhibits iodine uptake mediated by NIS, though with lower affinity. There are some limited but sufficient data regarding thiocyanate to potentially use in further strengthening the model's assumptions regarding coexposures. These data include measured thiocyanate exposures in various early pregnancy cohorts, including NHANES.

Stephen M. Roberts, Ph.D.

The assumption is valid — the issue is the extent to which the available data adequately reflect variability in exposure to other goitrogens. This is a source of uncertainty in the model, but not so great as to negate the utility of these data for model calibration.

Joanne F. Rovet, Ph.D.

I'm not too sure what this means.

DRAFT

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Question 9. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA conducted a three-step literature review, which identified 15 studies with information that could inform the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes.

Question 9A. Please comment on whether EPA has clearly identified the criteria to identify studies through each of the three steps of the literature review, and the adequacy of the strategy for conducting the literature search. Are these criteria scientifically supportable, and did EPA apply them properly?

Hugh A. Barton, Ph.D.

The strategy for the literature search and the criteria for categorizing the studies into three groups are clear and scientifically supported.

The search strategy initially appeared too narrow in that six additional references were added from the previous SAB review to the 49 identified through searching. Of the six, four were category 3 and thus found not to provide relevant information. Two were category 1, with one published in 1999 (before the 2000 – 2017 search period) and one in 2011, during the search period. Thus, the search appears to have been somewhat stronger than it initially appeared. But, if the search is updated, it may be worth considering whether other search terms or a broadening of the search time period would be beneficial.

Some commenters suggested that the criteria were not applied correctly in the determinations of categories, so EPA should review the decisions to insure they were appropriate.

Nancy Carrasco, M.D., M.S.

Although I am no expert on issues related to the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes, it seems to me that, yes, EPA has clearly identified the criteria for identifying relevant studies through each of the three steps of the literature review. The strategy for conducting the literature search appears to be adequate, to the best of my knowledge. I think the criteria employed by EPA are scientifically supportable and that EPA used them properly.

Jonathan Chevrier, Ph.D.

The literature review strategy is well-described, but some details are lacking. For instance, there is no information about the number of individuals who were involved at each step, whether more than one person reviewed the studies identified after running the searches (ideally there would be at least two people) and how disagreements were resolved.

The fact that some search strings were restricted to paper titles, while others were not, is somewhat puzzling and raises the possibility that some papers may have been missed. Google search can indeed generate an unreasonably large number of hits but PubMed is usually more

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restrictive when using boolean terms, which was confirmed to me when I used some of the search strings listed in the report. I also wonder why "thyroid" was not used as a search term. "T4" or "thyroxine" could miss some paper of interest.

Finally, the fact that ultimately only studies with significant results were considered does not seem appropriate. Such a strategy is likely to overstate the effects of perchlorate on neurodevelopment. It is important to note that statistical significance is a function of the magnitude of the association and sample size and so estimates from non-significant studies, though imprecise, still have value. Ideally, a summary estimate would be generated from the literature for different outcomes, but studies are not similar enough to combine estimates.

Claude Emond, Ph.D.

I think EPA did everything they could to extract from the literature all the data that were required from epidemiological studies.

Dale Hattis, Ph.D.

I have no difficulty and no suggestions for improvement of the document on these issues.

Angela M. Leung, M.D., M.Sc.

The EPA restricted the literature search to studies examining maternal serum FT4 or TT4 levels and offspring neurodevelopment published only after 2000 in order to focus on the most recent science. The Haddow 1999 study was excluded due to the year of publication, as well as the absence of maternal serum FT4 or TT4 levels in the study (the latter is erroneous though). Although it is reasonable to restrict by date of publication, the exclusion of studies that examined only maternal serum TSH concentrations may miss some important data. The Haddow study is a good example of a seminal piece of literature, critical toward a more complete understanding of this topic, that was excluded (or at least placed in Group 3) on this basis.

Overall, the search terms appear to be comprehensive in capturing the desired output.

Of note though, it is unclear why many studies older than the year 2000 were categorized into Group 3, when the search criteria were described in Section 5.1 to be restricted to those later than this cutoff date.

Stephen M. Roberts, Ph.D.

The search strategy used to identify key studies able to inform the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes is clearly described in the report. The search strategy to identify candidate papers, including search engines and search

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strings are listed, and the process of selecting the most useful studies through a three-step screening process is well described. The rationales for categorization decisions of specific papers is presented in tabular form which offers transparency to the analysis. The criteria for selection of the key studies is reasonable and scientifically appropriate.

Joanne F. Rovet, Ph.D.

This seems reasonable, although ultimately perhaps a bit too restrictive as some very good studies were eliminated from the final selection. A few critical references are missing (see above). Nevertheless, the quality of analysis was thorough, exhaustive, and very systematic. Unfortunately, most of the studies making the final cut were from Europe, particularly the Netherlands, which I believe has higher iodide sufficiency than the US.

DRAFT

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Question 9. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA conducted a three-step literature review, which identified 15 studies with information that could inform the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes.

Question 9B. Please also comment on the summary and characterization of the literature in Chapter 5 of the MCLG Approaches Report and identify any inaccuracies or mischaracterization of the studies.

Hugh A. Barton, Ph.D.

The descriptions of the literature were generally clear and application of the criteria for categorization appeared reasonable. Not having read the original literature, I cannot comment on the accuracy of these summaries. The section includes studies with findings of relationships between thyroid hormone levels and neurodevelopment and studies that do not find such relationships, or do not find relationships for some endpoints. It provides EPA's perspective on the overall database. In the document, EPA indicates that, based upon comments in previous peer reviews, they did not conduct a systematic review. EPA should consider whether a formal systematic review would strengthen their analysis.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

The summary and characterization of the literature in Chapter 5 appeared appropriate to me. However, I note that under column label "Effect Estimates" the note that "[β based on untransformed…]" suggests that beta coefficients are shown but odds ratios are sometimes shown (i.e. exponentiated betas). I suggest changing the note to "[Estimates based on untransformed…]". I note that indicating what estimates are shown (i.e. mean change in outcomes, odds ratios or other) would help clarify what is being shown.

Claude Emond, Ph.D.

No comment at this time.

Dale Hattis, Ph.D.

I have no difficulty and no suggestions for improvement of the document on these issues.

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Angela M. Leung, M.D., M.Sc.

The reference to T4 in the Oken 2009 study in Table 22 should be clarified as total T4. Other than this, along with the exception the Haddow 1999 study noted above, the summary and characterization of studies as listed in Tables 10-22 appear to be accurate.

Stephen M. Roberts, Ph.D.

Group 2 studies are summarized in tabular form in Chapter 5 and short narrative form in Appendix E; Group 1 studies are described in narrative form in Chapter 5, including tables with key data from these studies. The level of detail provided for both Group 1 and 2 studies is appropriate for the purposes of this report and I did not identify any inaccuracies or mischaracterizations.

Joanne F. Rovet, Ph.D.

This is quite well done and thorough. I was very impressed and appreciated seeing the data digitized for some of the studies. I also liked the evaluation (section 7.1) examining population shifts. I wonder too whether more might be said of the findings from studies that produced the opposite relations that were found and what these findings may be due to or mean.

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Question 10. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, MDI, PDI and reaction time) based on the measurement of fT4 during early pregnancy at weeks 12, 13 and 16.

Question 10A. Please comment on the assumptions, strengths and limitations of focusing on the five studies and associated neurodevelopmental end points to inform an MCLG, including but not limited to study design, evaluation of neurological endpoints, sample size, iodide nutrition status, potential confounders such as smoking, and study population.

Hugh A. Barton, Ph.D.

One concern is whether there would be a method to allow consideration of the findings of multiple studies, including those with negative findings (either overall or for specific measures, such as IQ or Bayley Scales MDI or PDI). There is mention of a couple of papers that provide meta-analysis, so there are a few studies that are sufficiently similar to be combined. It may be that evaluating the exposure-response using multiple studies is the best approach allowing some estimate of an average and variability.

Nancy Carrasco, M.D., M.S.

Again, although I am not an expert on these kinds of analyses, it seems to me that focusing on these five studies was appropriate and sound, even though it would have been better to have more than five studies, if they existed.

Jonathan Chevrier, Ph.D.

As mentioned above, selecting only studies that reported significant results is likely to overstate the relation between perchlorate and neurodevelopment. Assuming that results are unbiased and that each study sample was selected at random, results from each study represents a point on a distribution of possible results, centered on the true association. Because only one study could be selected for each outcome, it is unclear where published results lie on that distribution.

I think that it is important that EPA take into account the quality of the studies used as part of this exercise, but it is unclear to me whether this was done. A clear framework for the evaluation of such studies should be developed and applied. Some limitations include:

- Korevaar et al. controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should

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investigate the most appropriate functional form to inform decisions about transformation of fT4 values.

- Finken et al. also controlled for BMI in their fully-adjusted model and fit a regression over the entire range of fT4. They do not appear to have investigated functional forms other than a linear relation, although it would be reasonable to believe that fT4 may not affect child neurodevelopment over a certain (normal) range. Authors mention that they standardized fT4 values for the postmenstrual day at which sampling occurred but it is not clear how this was performed.

- Regression coefficients for the studies by Pop et al. were based on very small samples (n=22 and 57) and so it is unclear how reliable these coefficients are. Small studies are more likely to find extreme results and small studies with significant results are more likely to be published. In addition, my understanding is that the scatter plots that were used to derive regression coefficients were not adjusted for confounders. Finally, the predictive potential of Bayley scores at a young age (i.e. 6 months to 2 years) on neurodevelopment at older ages is unclear.

This said, studies by Korevaar et al. and Finken et al. have the advantage of having been conducted on relatively large samples and evaluated neurodevelopment in children aged 5-6 years. However, the fact that all of the studies measured fT4 via immunoassays, which can be biased by the concentration of T4-bound proteins, remains a notable limitation. The fact that no studies were conducted in a U.S. population is also a potential limitation.

Claude Emond, Ph.D.

No comment at this time.

Dale Hattis, Ph.D.

The covered studies are plenty to analyze the likely IQ response to perchlorate.

Angela M. Leung, M.D., M.Sc.

The report focuses on the results of five studies that demonstrate adverse neurocognitive effects of offspring of hypothyroxinemic women (based on serum FT4 concentrations as a continuous measure) during early pregnancy.

- **Study design**: Study designs were essentially identical, in which measurements of perchlorate, thyroid function, other analytes from banked maternal sera collected during early pregnancy were correlated to at least one measure of neurocognition in their offspring. In the absence of more prospective, adequately-powered studies (i.e., CATS trial), this is the only type of study design that can feasibly assess the longitudinal outcomes of interest many years later.

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- **Neurological endpoints**: This is commented briefly in Section 6.5.2 of the report. The neurocognitive outcomes among the offspring were measured at fairly disparate ages (range: 10 months to 10 years of age). The neurocognitive outcomes were also different and included IQ, reaction time, and psychomotor development. Although these are fairly reasonable differences, given the paucity of published data otherwise, it would be prudent to consult with a psychologist with expertise in childhood test measures and thyroidology to comment on these outcomes. As we know there is continuing development of different structural areas during postnatal neurogenesis (see Bernal J, PMID 17315033), further expertise is needed to correlate whether the adverse outcomes are reasonable with the timecourse of thyroid hormone-dependent neurogenesis.
- **Study size**: This is commented on briefly in Section 6.5.4 of the report. There was a wide variation in the sample sizes of the five included studies (number of mother-infant pairs): 22, 27, 57, 1765, and 3839. However, even though three of the studies were relatively small, significant associations between maternal hypothyroxinemia and adverse neurocognitive outcomes of interest were still observed. The report did not restrict studies based on small sample size alone.
- **Iodine status**: This is commented briefly in Section 6.5.3 of the report. Among the five studies, urinary iodine concentrations (as a marker of iodine status) were variably assessed. The Korevaar 2016 study (n=3839) assessed urinary iodine in a subset of 672 women and the Vermiglio 2004 study (n=27) measured urinary iodine in the full sample, but the remaining three studies did not at all. If urinary iodine concentrations are abnormally high or low (i.e. both directions outsides of the "adequate" range) in the datasets, adjustment for these values may reasonably alter the strength and/or directionality of the findings. However, as mentioned in question #5 above, there are limitations of using urinary iodine concentrations to interpret iodine status in a given individual. Iodine status is much more reliably measurable on the population level.
- **Potential confounders**: The number and type of potential confounders adjusted for in the five studies varied considerably, as is shown in the footnotes of Table 22.
- **Study population**: This is commented briefly in Section 6.5.1 of the report. The five studies were conducted mostly in The Netherlands (4 studies), and there was also one small study in Italy (Vermiglio 2004, n=27). Italy has historically been an iodine-deficient country, and although the Vermiglio study measured urinary iodine to categorize the 27 women into 16 who resided in an iodine-deficient region of the country vs 11 who resided in an iodine-sufficient region, the actual urinary iodine concentrations were not used, but rather they were categorical measures used in the analyses examining offspring IQ. The Netherlands has examined only pregnant women for population iodide status (www.ign.org), which in 2002-2006 was considered adequate. This information increases the reliability of the findings in the 4 studies arising from The Netherlands, in which only one measured and adjusted for urinary iodine in a small subset of the study sample.

Stephen M. Roberts, Ph.D.

The final selection of five studies was based principally on the availability of data in a form that could be used to describe the quantitative relationship between maternal fT4 and one or more endpoints related to neurodevelopment. Given the goal of including neurodevelopmental

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outcomes in a quantitative model, focusing on these studies is logical. Study designs were appropriate to provide the needed information. Smoking as a potential confounder was addressed in some but not all of the studies, and information on iodine nutritional status was available to varying extents among the studies. Limitations in information provided by these studies are discussed well in Section 6.5, and I am not aware of any additional limitations.

Joanne F. Rovet, Ph.D.

I sensed a naiveté in understanding the meaning of the endpoints and their relation to underlying brain function. Despite an excellent appendix describing the relevance of the two BSID versions for Dutch children, I sense some need for caution in interpreting these results. The Bayley scales are a measure of developmental appropriateness and how well the child has achieved the level relevant to peers, whereas Wechsler tests represent how well the child actually performs relative to population norms. Dutch children often score above American. It is interesting to note that the distribution of IQ scores for American children has a different shape and a different midpoint than for Canadian, hence a separate scoring system for the latter. All of these population differences should be understood when making predictions.

As for SDRT, this is an index often used to characterize children with attention disorders and doesn't represent intelligence. However, RT itself may be a gross proxy to intelligence. It is interesting to note too that effects of maternal hypothyroxinemia were mostly on non-verbal perceptual aspects of intelligence and not global IQ itself or verbal IQ. The nonverbal aspects of intelligence are usually subserved by more posterior brain regions that develop earlier than anterior and may receive their thyroid hormone via the choroid plexus.

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Question 10. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, MDI, PDI and reaction time) based on the measurement of fT4 during early pregnancy at weeks 12, 13 and 16.

Question 10B. Please comment on whether the chosen studies are sufficient in number, quality, and robustness for the purpose of informing the derivation of an MCLG.

Hugh A. Barton, Ph.D.

See comments on 10a.

Nancy Carrasco, M.D., M.S.

I think the studies chosen are sufficient for the purpose of informing the derivation of an MCLG, even though, as I indicated above, a larger number of studies, if available, would have been desirable.

Jonathan Chevrier, Ph.D.

It appears to me that the small number of studies linking fT4 with neurodevelopment and the lack of overlap between studies in terms of outcome are important limitations that will make it challenging to derive an MCLG.

Claude Emond, Ph.D.

The data available are enough in number, but may be eclectic when compared. The concept linking the reduction of fT4 to neurodevelopment is known; however, the variability between studies, particularly in regard of concentration measured, may require comparing the methodology used or refining the methodology. I think EPA did great, and more importantly the maximum amount with the information available from epidemiological studies.

Dale Hattis, Ph.D.

The covered studies are plenty to analyze the likely IQ response to perchlorate.

Angela M. Leung, M.D., M.Sc.

The remaining ten studies that also studied these and other neurodevelopmental endpoints, but which did not report significant associations, were not included for the purposes of a perchlorate MCLG derivation. Excluding these studies lessens the power of the total sample size and thus

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the ability to detect an association between maternal hypothyroxinemia and any of the offspring outcomes, but provides what may be a somewhat exaggerated estimate of the potential adverse effects of perchlorate exposure. This approach is more conservative, to which there are pros and cons of doing so, toward derivation of a perchlorate MCLG. With this approach, the goal is to minimize exposure to the lowest perchlorate concentration associated with any number of adverse outcomes.

I would favor the more liberal public health approach, which is inclusion of all available studies, whether they are positive or negative. Although the perchlorate MCLG may be higher, this latter approach would be consistent with using all available evidence to improve the scientific rigor of the proposed study question.

Stephen M. Roberts, Ph.D.

While one can always wish for more studies, more subjects, and more endpoints, the chosen studies are sufficient in number, quality, and robustness to inform the derivation of a MCLG.

Joanne F. Rovet, Ph.D.

I think this could have been improved by combining the results across the 5 studies using SD or Z-scores and the SD of RT scores (not SDRT) of the groups.

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Question 10. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, MDI, PDI and reaction time) based on the measurement of fT4 during early pregnancy at weeks 12, 13 and 16.

Question 10C. Please provide advice on reducing any identified limitations.

Hugh A. Barton, Ph.D.

See comments on 10a.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

Given the limitations that I noted above, should EPA decide to go ahead with this approach, I think that models should focus on the most robust studies, i.e. those of Korevaar et al. and Finken et al. but an attempt to integrate strong studies with negative results must be made. The re-analysis of the Korevaar et al. data may be the best avenue given that Finken analyzed data over the entire range and ignored potential nonlinearities. This analysis should not include gestational age at the time of fT4 measurement or BMI as confounders. If measurement error due to variation in gestational age when fT4 was measured is of concern, these values should be corrected to represent values at the same stage (e.g. based on a model relating gestational age and fT4). Also, a model stronger than the linear regression used by EPA would be based on a smoother which would avoid assuming a linear relation and reduce the influence of outliers or other particularly influential points on the prediction. EPA may want to consider asking Finken et al.'s data to re-analyze data over the lower range of fT4 and/or using smoothers without controlling for BMI.

Claude Emond, Ph.D.

No comment at this time.

Dale Hattis, Ph.D.

The covered studies are plenty to analyze the likely IQ response to perchlorate.

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Angela M. Leung, M.D., M.Sc.

It may be interesting to compare the model outputs if the remaining ten studies in Group 1 (that did not report a significant association between maternal hypothyroxinemia and at least one offspring neurocognitive measure) were included vs. not included in the further analyses.

Stephen M. Roberts, Ph.D.

I have no advice on reducing limitations, but as stated in response to the previous question, consider the studies adequate for the purpose of informing derivation of a MCLG.

Joanne F. Rovet, Ph.D.

I would have liked more discussion on other thyroid disruptors.

DRAFT

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Question 11. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

Question 11A. Please comment on the assumptions, strengths, and limitations of using the regression analyses to inform the relationship between thyroid hormone levels and neurodevelopmental outcomes. Please also comment on the various functional forms of the regression equations (e.g. linear, log-linear, quadratic) in each of the relationships.

Hugh A. Barton, Ph.D.

Using regression analysis to describe exposure-response appears reasonable. It does not appear appropriate to try to apply some form of PKPD modeling to analyze these results.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

As I noted below, the fact that different functional forms were assumed by different studies presents some challenges. First, the distributional form of independent variables should not influence decisions to transform them, as they have little effects on the distribution of residuals in least square (linear) regression. Functional form should either be based on known "exposure"-response relationships or on examination of the data and determination of the form that fits the data best.

Although a quadratic form fit the data by Korevaar et al. well over the entire range of fT4 (and the fact that this relation makes biological sense), I support EPA's suggestion to focus on data at the lower range of fT4 to develop their prediction model. As noted above, I would suggest that EPA not force any functional form on the data but simply apply a smoother. This will avoid the question of the range of fT4 values over which the model should be run and potentially different results that could be obtained depending on the range selected

Claude Emond, Ph.D.

The analysis of data, using different regression equations, is not unusual.

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Dale Hattis, Ph.D.

As indicated earlier, I believe the regression analyses can and should be improved by substituting Michaelis-Menten transforms for the log(perchlorate) levels in the analyses. See the response to question #3 above.

Angela M. Leung, M.D., M.Sc.

The use of multivariable linear regression would appear to be an appropriate statistical analysis based on the available data, but I defer to the other reviewers with modeling expertise. I have reviewed the summary data presented in Tables 38 and 39, but am unable to comment further on the various functional forms of the regression equations.

Stephen M. Roberts, Ph.D.

The regression analysis is a logical approach to quantifying the relationship between maternal fT4 and various neurodevelopmental deficits. There are a number of limitations and uncertainties associated with this approach that are candidly summarized in Section 6.5.6, including the uncertainties associated with the form of the regression equations. I agree with these limitations and have no additional limitations to add.

Joanne F. Rovet, Ph.D.

This is fine but maybe the meaning of the numbers could be better explained for those less familiar with this approach. Also, the p-values should be given or identified consistently. I think the text could better explain the contents of the table.

DRAFT

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Question 11. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

Question 11B. Please identify additional data or analyses EPA could use to quantify the relationship between thyroid hormone levels and neurodevelopmental effects, including how this information would be expected to improve the analysis.

Hugh A. Barton, Ph.D.

None identified.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

See responses above.

Claude Emond, Ph.D.

No further comment.

Dale Hattis, Ph.D.

The use of a Michalis-Menten formulation as indicated in (a) above and in the response to question 3 will provide a more biologically plausible relationship to fit. Because it carries an extra parameter (Km) it will also likely lead to a better fit to the empirical data although a full analysis will need to adjust for this in judging whether the fit is improved enough to justify the added complexity of the model.

Angela M. Leung, M.D., M.Sc.

There are some scant data regarding structural brain size differences in offspring born to hypothyroid women by Dr. Rovet's group, but the classifications of exposure do not appear to have been based on maternal serum FT4 concentrations. There may be additional data regarding morphological brain differences among offspring using maternal FT4 in the future.

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Stephen M. Roberts, Ph.D.

I am not aware of any additional data or analyses that could be used to quantify the relationship between thyroid hormone levels and neurodevelopmental effects.

Joanne F. Rovet, Ph.D.

The use of cut-points might be included. The categorical approach needs better explaining.

DRAFT

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Question 11. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

Question 11C. Please comment on whether there is a magnitude of change in fT4 below which the relationship between fT4 and neurodevelopmental effects should not be used because it is too uncertain.

Hugh A. Barton, Ph.D.

No comment.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

A change that is smaller than the level of precision of instruments used to measure fT4 would not be reliable. Changes that can otherwise be detected by instruments are of interest.

Claude Emond, Ph.D.

There are 2 things here. First, I agree that the magnitude reported is uncertain; however, it provides a level of change associated with doses. It should indicate the confidence we have with the value.

Dale Hattis, Ph.D.

I believe there is no such lower limit to the applicability of the analysis.

Angela M. Leung, M.D., M.Sc.

This is commented on briefly in Section 6.5.6 and Table 34 of the report. The reasoning provided, that worse neurodevelopmental outcomes would be biologically plausible and expected with even lower maternal serum FT4 concentrations, is reasonable, and I would not think there would be a specific FT4 cutoff corresponding to a loss of effect.

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Stephen M. Roberts, Ph.D.

I have not yet formed an opinion on this question and look forward to discussion with other panel members during the face-to-face meeting in formulating my response.

Joanne F. Rovet, Ph.D.

I didn't understand why the 50th percentile values were used.

DRAFT

ED_005043_00063236-00063

Question 11. Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

Question 11D. Please comment on whether other studies that were identified in the literature search (e.g., studies that found categorical relationships between fT4 and neurodevelopmental outcomes, studies that found effects but lacked statistical significance, studies that did not find an effect) could be utilized to quantitatively characterize the relationship between fT4 and neurodevelopmental outcomes or inform uncertainty associated with the analysis presented.

Hugh A. Barton, Ph.D.

It does not seem feasible to develop an exposure response from the categorical findings, but they can be used, as done by EPA, to evaluate qualitatively whether there is consistency between categorical and continuous analyses.

Nancy Carrasco, M.D., M.S.

No comment.

Jonathan Chevrier, Ph.D.

I think that it is important to consider studies that found results that were not statistically significant, especially if sample size is of reasonable size and risk of bias is low. I recommend EPA focus on effect size rather than statistical significance. Studies of good quality that found no effect also have value as they can help estimate the true population values if multiple studies with similar outcomes can be combined. Ideally, multiple studies would be combined in an overall estimate in a meta-analysis together with a confidence interval and this value would be used to predict the impact of perchlorate, but too few studies can be combined in this case.

Claude Emond, Ph.D.

I am not aware to any other study, published or not.

Dale Hattis, Ph.D.

My literature search did not identify additional helpful studies.

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Angela M. Leung, M.D., M.Sc.

Please also see my comments to Questions #10b and 10c. The literature search produced ten studies (that assessed maternal serum FT4 concentrations as a continuous measure which did not observe an adverse effect on offspring neurocognition), as well as those in Group 2 that assessed serum FT4 as categorical measures. Although their inclusion may not necessarily be recommended in the final model, comparison of the estimated effects on the various neurocognitive outcomes with and without these may indeed inform the degree of uncertainty inherent in the present model. Several of the studies in Group 2 were able to demonstrate significant adverse outcomes (Berbel 2009 as one excellent example), and also their more global nature would help support the generalizability of the present model.

Stephen M. Roberts, Ph.D.

Data from studies that found no effect or effects that lacked statistical significance could in theory contribute to a quantitative characterization of the relationship between fT4 and neurodevelopmental outcomes, but the approach would need to be considered carefully. As the report points out, the absence of an effect (or a significant effect) in some studies may be due to range of fT4 considered. Combining studies that are dissimilar in critical ways would confound rather than improve the derivation of a quantitative maternal fT4-neurodevelopment outcomes relationship. Studies finding categorical relationships can be used to inform uncertainty with the analysis presented.

Joanne F. Rovet, Ph.D.

Certainly, the CATS study needs to be included. I think the list otherwise was quite complete, but I would have liked more discussion or further highlighting of the Craig study, given it is American and from a very reputable group. I would have liked more discussion on behavioral outcomes, beyond cognitive, such as ADHD and autism and their increased incidence in the population. Author(s) need to include the work of S. Anderson of Denmark on fetal programming of later mental illness and how perchlorate might contribute to this.

DRAFT

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Question 12. Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes. Please comment on the assumptions, strengths and limitations associated with the population-based approach that is focused on a shift in the proportion of the population that could be considered hypothyroxinemic.

Hugh A. Barton, Ph.D.

This is an appropriate approach for consideration. However, it has the disadvantage of appearing to be focused on potentially transient changes in thyroid hormone levels that one could debate whether the effects are adverse. For the two-stage approach, the end point is clearly adverse; that is, neurodevelopmental deficits in offspring of women who had low thyroid hormone levels. There may be a significant risk communication advantage to having a clearly adverse endpoint as the basis for the MCLG analysis rather than changes in thyroid hormone proportions in the population.

Nancy Carrasco, M.D., M.S.

This topic is outside my area of expertise. I am unable to provide any comments on it.

Jonathan Chevrier, Ph.D.

I believe that this approach has value. Hypothyroxinemia has the potential to impact numerous systems and health outcomes and focusing only on neurodevelopment has the disadvantage of ignoring other health effects of hyothyroxinemia.

Claude Emond, Ph.D.

No comment.

Dale Hattis, Ph.D.

I think the precise definition of "hypothyroxemic" has nothing to do with the real effects of perchlorate on offspring IQ and other relevant parameters of effect. The only relevance is how the medical community reacts with "cases" of "hypothyroxemia" in terms of treatment.

Angela M. Leung, M.D., M.Sc.

This is a reasonable approach to provide a perhaps rough estimate of the magnitude of the impact of perchlorate on a population level, but assumes that there must be an allowable proportion of the population in which maternal hypothyroxinemia associated with potential later adverse outcomes is acceptable. This is in line with some public health perspectives, in which

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interventions are implemented to benefit the vast majority (but not all) of those at risk in a given population.

As the report describes in detail (Section 7.2), there are also many assumptions and uncertainties toward deriving this estimate, including but not limited to the definition of maternal hypothyroxinemia during pregnancy; the limitation of the analyses to gestation weeks 12/13/16 since neurogenesis begins as early as gestational week 3; and the choice of what constitutes an allowable hypothyroxinemic proportion of the population.

With both approaches, there are still issues surrounding the definition of adequate iodine status as noted previously (Question #5); the response of TSH to varying degrees of low iodine, low FT4 levels, and perchlorate (separately and additively); and uncertainties regarding duration of perchlorate exposure.

Stephen M. Roberts, Ph.D.

The population-based approach relies upon BBDR modeling to predict the relationship between perchlorate dose and fT4, and thus has all of the strengths and limitations associated with that modeling in common with the two-stage approach. It avoids, however, additional uncertainties associated with extending the model to predict neurodevelopmental outcomes, relying instead on the premise that increasing the percentage of the population of pregnant women that is hypothyroxinemic increases the number of fetuses at risk. A population-based approach also simplifies somewhat estimates of the number of people that might benefit from management of perchlorate in drinking water to specific concentrations. Also, it is supported directly by studies showing, through categorical analysis, a relationship between hypothyroxinemia and increased risk of adverse neurodevelopmental effects. A limitation in this approach is that the explicit endpoint (a decrease in fT4 levels) is not an adverse effect per se, but is instead a precursor effect in a specific population. It is not a scientific limitation, but rather a communication challenge when explaining the approach to some audiences.

Joanne F. Rovet, Ph.D.

I like this approach. I think increasing the population frequency of hypothyroxinemia is a relevant outcome to assess following perchlorate exposure in pregnancy.

On cardiovascular disease, might there be a comparable effect in the offspring, that should be studied.

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Question 13. Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes. Hypothyroxinemia is the condition of having an abnormally low level of T4 in the blood and TSH is in the normal range, and in diagnosing this condition the threshold for "abnormally low" is often selected to be the 2.5th, 5th or 10th percentile of the population fT4 distribution. Because the BBDR model can be calibrated to any given percentile, but does not predict the distribution of fT4 levels, it was necessary to derive a fT4 distribution to identify a hypothyroxinemic threshold. EPA assumed a lognormal distribution with a Geometric Standard Deviation based on 2 to 3 studies depending on the gestational week. There is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. For example, some of the analyses show larger unit changes with increasing percentiles of fT4 in most analyses (See tables 24, 30, 31, 32, 33 and Section 6.5.6 of the MCLG Approaches Report). Please comment on the assumptions, strengths and limitations of the derived fT4 distribution for the purposes of this analysis.

Hugh A. Barton, Ph.D.

No comments, as this is outside the reviewer's area of expertise.

Nancy Carrasco, M.D., M.S.

This topic is outside my area of expertise. I am unable to provide any comments on it.

Jonathan Chevrier, Ph.D.

The fact that the model predicts stronger effects at higher levels of fT4 is a major limitation that gives me pause in the use of the model with its current specifications because it makes little biological sense. This may be due to the fact that fT4 was assumed to be log-normally distributed, which does not agree with my own experience. I think that EPA should evaluate the impact of this choice of a distribution and revert to a normal distribution if models generate results that agree better with our understanding of the biology – i.e. that effects of perchlorate on child neurodevelopment should be stronger among women with low fT4 to begin with. One way or another the discrepancy between the model's results and current knowledge must be reconciled.

Claude Emond, Ph.D.

The strategy used by the EPA was probably the best, considering the availability of the information. It is usually not appropriate to juxtapose different studies, but here it gives us at least a range of information.

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Dale Hattis, Ph.D.

I have already commented in some detail on the expected interindividual variability in fT4 levels. See my response to question 7c.

Angela M. Leung, M.D., M.Sc.

The 2.5th, 5th, and 10th percentiles have been the conventional choices in defining a maternal serum FT4 concentration for defining hypothyroxinemia during pregnancy. Section 6.5.6 of the report describes the uncertainties surrounding the selection of a specific cutoff. Negro et al. (PMID 21247845) has also recently reviewed this topic. The current report has selected a 10th percentile FT4 cutoff, and thus presents what may be a relatively higher proportion of women with hypothyroxinemia compared to the lower cutpoints (i.e. the American Thyroid Association defines the condition as the lowest 2.5th or 5th percentile of a given population). I defer to the other reviewers regarding the model code of the derived FT4 distribution.

Stephen M. Roberts, Ph.D.

I have not yet formed an opinion on this question and look forward to discussion with other panel members during the face-to-face meeting in formulating my response.

Joanne F. Rovet, Ph.D.

My only comment is whether the 10th percentile is too high to be considered "hypothyroxinemia", in the sense of being a clinical condition.

DRAFT

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Question 14. Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes. Please comment on the strengths and limitations of the two-stage approach versus the alternative population-based approach to inform the derivation of an MCLG.

Hugh A. Barton, Ph.D.

Both approaches are attractive. It is difficult to compare the strengths and limitations of the two methods, as the probabilistic analysis involves many technical elements this reviewer cannot evaluate. While population approaches are desirable, and often model reviewers are uncomfortable when only an average result is presented, it is also frequently true that there is greater uncertainty involved in adequately describing population variability as compared to the population average behavior.

As noted in response to question 12, there may be a significant risk communication advantage to having a clearly adverse endpoint as the basis for the MCLG analysis rather than changes in thyroid hormone proportions in the population.

Nancy Carrasco, M.D., M.S.

This topic is outside my area of expertise. I am unable to provide any comments on it.

Jonathan Chevrier, Ph.D.

The population-based approach certainly has the advantage of relying on fewer assumptions, but it is not clear what threshold should be used to define hypothyroxinemia. The two-stage approach has the advantage of predicting health effects, but the number of studies to derive estimates is small and it is unclear how the negative studies can be integrated in this framework.

A limitation of both methods is that they do not appear to consider the uncertainty of the BBDR model. Estimates are simply taken as is and, in the case of the two-stage model, applied to the confidence intervals of the studies of fT4 and neurodevelopment.

Claude Emond, Ph.D.

No comment.

Dale Hattis, Ph.D.

The MCLG is mostly a policy position. There are, as far as I can see, no real thresholds in the relationships described.

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Angela M. Leung, M.D., M.Sc.

Both approaches have their advantages and disadvantages. The two-stage approach is inherently based on more granular individual data, albeit from only a few large datasets drawn primarily from The Netherlands, to estimate discretely decreased maternal serum FT4 levels following perchlorate exposure to result in later adverse offspring neurocognitive outcomes, and thus in theory offers a more stringent estimate of the risks of perchlorate exposure. The alternative population-based approach uses a conventional public health perspective to estimate an allowable proportion of pregnant women to be at potential risk for the adverse offspring effects in order to potentially implement an intervention to decrease risks for the vast majority, but not all, of those who may develop the adverse outcome.

Stephen M. Roberts, Ph.D.

The two-stage approach is consistent with the vision of the 2013 SAB, which uses a model capable of predicting quantitatively neurobehavioral outcomes in relation to perchlorate exposure. Although additional refinements in the model are possible, especially as new information becomes available, all of the component pieces are in place. The model is informed by, and calibrated to the extent possible using, human data, which is a considerable strength. The alternative population-based approach has many of the same strengths as the two-stage approach, but stops short of quantifying neurobehavioral outcomes based upon perchlorate effects on thyroid hormone levels. The strengths and weaknesses of this approach are discussed in the response to Question 12.

Joanne F. Rovet, Ph.D.

I am not sure what is meant by the alternative.

DRAFT

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Question 15. <u>Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes</u>. EPA has developed a two-stage approach linking the revised BBDR model results with quantitative information on neurodevelopmental outcomes from epidemiological studies. Please comment on the utility of the this two-stage approach for predicting potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes in the population at varying levels of iodide intake. Please comment on whether there are better strategies for estimating the potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes that are likely to be more scientifically defensible than the approaches presented (e.g. Appendix C estimates IQ impact directly from perchlorate exposure using Steinmaus et al. and Korevaar et al., or potentially some alternative studies). If an alternative approach would be more appropriate, please outline specifically how the approach might be developed given the current available state-of-the-science and data.

Hugh A. Barton, Ph.D.

Given the limitations of the data, the two approaches considered seem stronger than using the results of a single study to relate perchlorate exposure directly to neurodevelopmental outcomes.

Nancy Carrasco, M.D., M.S.

This topic is outside my area of expertise. I am unable to provide any comments on it.

Jonathan Chevrier, Ph.D.

I commend EPA for engaging in such a complex enterprise. In my opinion, this approach would have greater value if a larger number of studies were available that allowed for the computation of a summary estimate. Although evidence for an impact of maternal fT4 during early pregnancy on child neurodevelopment is convincing, there remains much uncertainty regarding the precise association (in terms of strength and functional form) between these variables. Although apparently not quantified, there is also uncertainty associated with the BBDR model.

The limitations that I mentioned above also apply to the approach presented in Appendix C and so would not help in determining which approach is best. I also note that in this approach log-linear relations were assumed for both models, but I am not sure whether another function fit the data better and, here again, smoothers could avoid questions about functional form. In addition, I am not clear why, if epidemiological studies are to be used to derive an MCLG, research investigating relations between prenatal exposure to perchlorate and child neurodevelopment were not used. Attempting to combine results from different studies conducted in different populations certainly adds to the uncertainty and potential for bias.

This said, whether the two-stage or the method presented in Appendix C is based on the confidence that one puts into the BBDR model relative to epidemiological studies, I think that the method from Appendix C could have some value if a large number of studies was meta-analyzed. However, in this particular case only one study was used to evaluate each relation

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which is insufficient to predict effects with any reasonable level of certainty. I would thus favor the two-stage approach.

Claude Emond, Ph.D.

No comment.

Dale Hattis, Ph.D.

I think use of the Steinmaus and Korevaar data is the best approach that can be done at present.

Angela M. Leung, M.D., M.Sc.

The use of the two-stage approach, linking the current model to quantitative data from available studies, is reasonable for predicting the population impact of environmental perchlorate exposure. Although the quantitative data are relatively few in number and from primarily a single country, and thus could be improved to add power and generalizability, they do represent probably what is currently known about this evolving topic. Future studies that specifically examine the perchlorate content of banked biospecimens collected during early pregnancy and correlated with offspring neurodevelopmental outcomes would offer more direct and confirmatory evidence of these relationships. Furthermore, animal models may offer additional mechanistic insight of perhaps independent effects of perchlorate on neurogenesis apart from decreasing maternal thyroid hormone levels.

Stephen M. Roberts, Ph.D.

Alternative approaches such as the examples in Appendix C would not be more appropriate than using BBDR modeling. Based upon current understanding of thyroid physiology and the MOA for perchlorate, susceptibility to development of adverse neurodevelopmental outcomes from perchlorate exposure is complex and can be influenced by a variety of factors (e.g., iodide intake, co-exposure to other goitrogens, gestational age). BBDR modeling allows these factors to be addressed explicitly and quantitatively in establishing a safe exposure level for perchlorate. Through modeling, a variety of subpopulations and exposure scenarios of interest can be evaluated. This is more scientifically defensible than basing a MCLG on observations from a single study such as the Steinmaus et al. example in Appendix C. Aside from limitations of this specific study (lack of concurrent timing of measurements of perchlorate exposure and fT4, estimation of perchlorate exposure from a single spot urine sample, measurement of fT4 in the second rather than first trimester, and others), whenever a single study is used there is uncertainty whether the study population adequately represents other populations of interest/concern.

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Joanne F. Rovet, Ph.D.

I like this approach and consider it to be state-of-the-art in relation to what is currently available. It represents a significant improvement over the previous modelling approach.

DRAFT

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V. SPECIFIC OBSERVATIONS ON REPORT (VOLUME 1)

Hugh A. Barton, Ph.D.

Specific Observations on Report (Volume 1) - *Hugh A. Barton, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
2-2	2	The point of this paragraph is unclear.
2-5	2 of 2.4	Did NRC consider inhibition of iodide uptake nonadverse no matter how much inhibition or were they saying that low percentage inhibition would be nonadverse? Or, is that not clear?
3-5	Sec 3.2	Merrill et al. 2005 missing from reference list
5-18	Table 12	What does N/A stand for?

Nancy Carrasco, M.D., M.S.

Specific Observations on Report (Volume 1) - *Nancy Carrasco, M.D., M.S.*		
Page	**Paragraph**	**Comment or Question**
1-2	4	"However, it must be noted that, because the adult euthyroid human thyroid contains several months of T4 stored in the colloid,.." The claim that the human thyroid stores several months' worth of T4 is a very significant one, yet no reference is provided. Also, a more precise time frame should be given.
8-1	3	"It must be noted that, because the adult euthyroid human thyroid contains several months of T4 stored in the colloid, ..." Here too, there is no reference.
3-13	1	"This likely occurs because the half-life of (organified) iodine in the adult thyroid is around six months." Once again, no reference is given.
1-1	4	"Ingestion exposures are of concern because perchlorate is easily and almost completely absorbed from the gastrointestinal tract (Srinivasan & Viraraghavan, 2009)." In this case, the reference given is a review, and once I located the relevant text in the review, I discovered that there was no reference to a primary research article.
2-7	3	"There is evidence from cell culture work that perchlorate is actively transported into the thyroid gland and this transport may be enhanced by increasing TSH and reduced in a dose-dependent manner by iodide (Tran et al., 2008). This active transport is potentially due to the upregulation of NIS (Hussein, Abbas, El Wakil, Elsamanoudy, & El Aziz, 2012)."

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Specific Observations on Report (Volume 1) - *Nancy Carrasco, M.D., M.S.*		
Page	**Paragraph**	**Comment or Question**
		This text is somewhat misleading. The evidence that perchlorate is actively transported into the thyroid gland is not limited to results from cell culture work. There is in vivo evidence published in 1959 (Anbar et al.) from the thyroid glands of rabbits and rats, and data showing NIS-mediated perchlorate transport into the milk in rat dams [Dohán et al., (2009) PNAS]. It is puzzling that the latter reference was not included. The authors use a systems biology approach to quantitate the inhibition of NIS-mediated I- transport at different concentrations of perchlorate.
3-3	1	"In particular, a decrease in fT4 is predicted to increase blood TSH, the response to which is an increase in the thyroid NIS activity and production rate constants for T4 and T3." This statement is not accurate. The direct response to an increase in TSH is higher NIS expression: TSH does not directly stimulate NIS activity. NIS activity increases only as a result of higher NIS expression
3-4	1	"Partitioning of perchlorate into red blood cells and binding to plasma protein are included in this model, unlike that of Lumen et al. (2013)." What is the evidence that perchlorate partitions into red blood cells? The plasma membrane is not permeable to perchlorate, which is an anion. Thus, NIS is required for perchlorate to be translocated across the plasma membrane, and NIS is not expressed in erythrocytes. Also, what is the evidence that perchlorate binds to plasma proteins?
3-5	2	"The Vmax for NIS-mediated uptake is also increased during pregnancy based on independent data." It is not clear what the evidence for this claim is, as no reference is given. What are the independent data mentioned?
3-5	2	"The perchlorate sub-model is analogous to that of the iodide model and describes the assumed mechanism of action for perchlorate. That is, once perchlorate is consumed it is distributed throughout the body, including to the thyroid plasma, where it can bind to NIS, which inhibits the uptake of iodide." This statement is inaccurate. Perchlorate does not "distribute to the thyroid plasma, where it can bind to NIS, which inhibits the uptake of iodide." Rather, perchlorate binds to an anion binding site on NIS, after which NIS translocates the perchlorate into the cytosol, thus preventing iodide from binding to NIS and being translocated into the cell.

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Specific Observations on Report (Volume 1) - *Nancy Carrasco, M.D., M.S.*		
Page	**Paragraph**	**Comment or Question**
2-4	2	"Conditions of low maternal iodine may also cause fetal thyroid function to be impacted once it begins, thereby putting the fetus at risk of developing hypothyroxinemia due to the lack of iodine coming from the mother to create its own thyroid hormone." This statement should be reworded for clarity: Low maternal iodine may also impair thyroid function once it begins, thereby putting the fetus at risk of developing hypothyroxinemia because it does not have enough iodine with which to synthesize its own thyroid hormone(s).
3-5	Table 1	"..that is adjusted for NIS-mediated uptake in skin and mammary glands" What is the evidence that there is NIS-mediated I- uptake in the skin? And regarding the mammary gland, NIS-mediated I- transport has been reported in the lactating mammary gland only, not in the non-lactating mammary gland. This point needs to be made clear.
3-11	Figure 5	How long did the perchlorate exposure last that yielded the data shown in Figure 5?
3-15	4	"The higher PC for perchlorate (80% increase in perchlorate ROB coefficient) reflects the higher ratio of Vmax/Km for NIS-mediated transport into mammary and skin for perchlorate versus iodide. The BBDR model assumes this type of distributional impact of NIS uptake is plausible; however, it has not been evaluated using empirical data." Contrary to what this statement suggests, the NIS Vmax and Km for perchlorate have actually been determined experimentally (Dohán et al., PNAS).
3-16	2	"Al-Rasheed et al. (2015) identified several variations in the DNA sequence characterizing the NIS gene as a potential variable influencing the development of differentiated thyroid cancer. While these data are not directly informative within the context of perchlorate, it demonstrates that variability in the NIS gene structure exists and may plausibly represent an important factor rendering individuals more or less sensitive to perchlorate exposure." This statement is misleading and inaccurate. The results presented in the paper cited do not indicate that individuals may be more or less sensitive to perchlorate exposure. This is a candidate gene study conducted in a very small cohort. Studies of this type, including this one, were carried out 10 years ago without population stratification or multiple testing correction. More

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Specific Observations on Report (Volume 1) - *Nancy Carrasco, M.D., M.S.*		
Page	**Paragraph**	**Comment or Question**
		importantly, of the 5 SNPs, only one is in an exon, and it is a silent mutation, as the codon still codes for cysteine. Three SNPs are in introns and the last SNP is in the 3' UTR (untranslated region). Therefore, none of the SNPs has any impact or effect on the NIS amino acid sequence or on NIS activity.
3-17	1	"The association between perchlorate and diminished T4 in the face of elevated TSH (Steinmaus, et al., 2013; Steinmaus, et al., 2007; Blount et al. 2005) suggests that certain segments of the population (low iodide, smokers) respond more weakly than others." The interpretation of the report cited is not correct. The findings presented in this paper do not suggest variability in certain segments of the population. From the way that the molecular mechanism of NIS functions, it follows that when people have low plasma iodide concentrations, there will be more pronounced inhibition by perchlorate. The effect observed in smokers is due to the high concentrations of thiocyanate that smokers have in their plasma. Like perchlorate, thiocyanate is a NIS inhibitor and a NIS substrate.
3-18	2	"Because it assumes euthyroid status, it does not, for example, address thyroiditis, which is caused by the production of thyroid autoantibodies (e.g., Hashimoto's Disease) and is a relatively common condition that may involve impaired iodide uptake across the NIS and in some individuals, may result in reduced production of T4." This statement is incorrect. Hashimoto's disease is the most common (not a relatively common) cause of hypothyroidism in the US. Therefore, it is not surprising that patients with Hashimoto's disease have lower levels of thyroid hormones.
3-18	2	"Brent (2010) raises the possibility that perchlorate and similar environmental exposures could increase the risk for Hashimoto's Disease." It is not clear why this statement was included in the report. The Brent paper cited does not even mention Hashimoto's disease.
3-5	2	"This inhibition (of NIS by perchlorate) reduces the thyroid's stores of organified iodide, and hence decreases the rate of formation and release of T3 and T4. As fT4 levels decline, the predicted concentration of TSH increases, thereby stimulating iodide uptake and thyroid hormone production, allowing for a partial compensation for the inhibition: the resulting decline in fT4 is less than it would be in the absence of this mechanism."

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Specific Observations on Report (Volume 1) - *Nancy Carrasco, M.D., M.S.*		
Page	**Paragraph**	**Comment or Question**
		This statement is conceptually incorrect, because it mistakenly assumes that a rise in TSH will result in increased iodide uptake and thyroid hormone production even in the continuous presence of perchlorate. What actually happens is that, as long as perchlorate is present, even a higher number of NIS molecules at the plasma membrane will not transport more iodide; instead, they will continue to transport more perchlorate, and there will be no compensation whatsoever for the inhibition. Moreover, nowhere in the report is it explicitly stated that perchlorate inhibits NIS-mediated iodide transport because perchlorate itself is translocated by NIS as a substrate. Mechanistically and pathophysiologically, there is a very important difference between an inhibitor being a blocker and an inhibitor being a substrate. Perchlorate is actively transported by NIS; this means that when perchlorate is present, it will be accumulated in all the tissues where NIS is expressed, including the thyroid, salivary glands, and stomach—and, critically, the lactating breast. In other words, if a mother who is breastfeeding is exposed to water contaminated with high concentrations of perchlorate, she will produce lower levels of thyroid hormones, and her newborn will receive perchlorate in the maternal milk in addition to receiving less iodide. This twofold harm will cause the newborn to synthesize thyroid hormones at lower levels at precisely the stage of life at which (s)he is most sensitive to inadequate thyroid hormone levels, given that thyroid hormones play a crucial role in the development and maturation of the central nervous system postnatally.

Jonathan Chevrier, Ph.D.

Specific Observations on Report (Volume 1) - *Jonathan Chevrier, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
2-2	2	The last sentence of this paragraph appears to suggest that higher total T4 will result in lower TSH. Is this correct? This would suggest that bound T4 can be detected by thyroid receptors in the pituitary gland and hypothalamus. I suggest that the sentence be re-phrased. The description of this phenomenon in section 2.2 (page 2-3 to 2-4) is more accurate. It is also unclear why this information is repeated in contiguous paragraphs.
2-5	1	The main effect of thyroid peroxidase (TPO) with regards to hypothyroidism and TPO antibodies is to catalyze 1) the iodination of tyrosine residues and 2) the coupling of iodotyrosine residues in thyroglobulin to form T4 and T3. The conversion of T4 to T3 is primarily handled by iodinases, I would also recommend using a textbook reference rather than a web page

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Specific Observations on Report (Volume 1) - *Jonathan Chevrier, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
		developed for the general public (which is improperly cited in the reference list). Webner and Ignmars' The Thyroid may work for that. Another option is Ruf J and Carayon P (2006) Arch Biochem Biophys; 445(2): 269-277.
3-2	2, last sentence	This sentence appears to be important but was confusing to me. Does this sentence mean that only exposure levels causing fT4 blood concentrations to be reduced at levels that would not be anticipated to trigger an increase in TSH were considered? If so, it appears to me that a better justification for this decision is warranted.
Throughout document		The terms iodine and iodide appear to be used alternatively throughout the document, which can be confusing/distracting. This sometimes happens in the same paragraph, for instance, the last complete sentence of page 3-9 and the sentence beginning on the last line of that same page.
4-2	1	It is not entirely clear to me how GSDs were back-calculated. The use of an Excel function is not necessary. Values simply need to be logged, an SD of the logged values calculated and then the SD to be exponentiated using the base of the log used for the initial transformation to compute the GSD. Essentially do I understand that 1) data were log-transformed and SDs were calculated, 2) these values were averaged across study populations, and 3) the average values were exponentiated using the base of the log used in step 1? I think this needs to be clarified. This brings another important concern. The standard deviation of combined populations is not equal to the (weighted) average of their standard deviations. The proper formula is: $$\sum_{j=1}^{n}(\overline{x_j}-\bar{x})^2 = \sqrt{\frac{\sum_{i=1}^{g} n_i\sigma_i^2 + \sum_{i=1}^{g} n_i(\overline{x_i}-\bar{x})^2}{\sum_{i=1}^{g} n_i}}$$ Where g is the number of populations, n_i is the sample size of population i, $x(bar)_i$ is the mean for population i, σ_i is the standard deviation for population i, and x(bar) is the overall average. This would need to be calculated on logged values and then exponentiated. Also, do I understand that data from the Mannisto study were included twice to calculate the 12-13 week GSD values? The fact that these data are not independent needs to be considered in computing these statistics.

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Specific Observations on Report (Volume 1) - *Jonathan Chevrier, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
		In addition, combining these populations requires strong assumptions, i.e. that there is a single population with overall GM and GSD from which each study was sampled. Is this a correct assumption? My understanding is that the distribution of thyroid hormone is population-specific. If that is the case, is it appropriate to combine data from different populations? The fact that no data from a US population is available should be noted as a limitation. Finally, was log-normal distribution expected for fT4? My own experience is that fT4 is consistently normally distributed. One thing to keep in mind is that immunoassays were used by all studies to measure fT4. Several studies have shown that immunoassays could be biased by the concentration of T4-bound proteins and that physical separation by equilibrium dialysis or ultrafiltration were gold standards to measure fT4. Could this or other factors explain such a skewed distribution of fT4? Also, the use of immunoassays to measure fT4 in the studies used should be considered a limitation.
4-2	Last	Last sentence: I don't understand how GSDs can be used to represent medians.
4-3	1	I did not understand this paragraph. I do not see why a separate GSD needs to be calculated for the low-iodine group and why standard deviations are compared between the 2.5th and 50th percentiles vs 50th and 97.5th percentiles. Certainly, reducing the GSD at lower levels of iodine intake would result in less extreme estimates of fT4 and, presumably, weaker effects of perchlorate than would otherwise be estimated by keeping the GSD constant. I also do not understand how the fT4 distributions were computed for different perchlorate exposure levels.
4-4	Table 6	Is the exposure level or the internal dose of perchlorate represented here?
4-6	1	I think that it is important to mention the consequences of assuming a log-normal distribution over a normal distribution. Presumably, the impact of perchlorate will be estimated to be smaller in the low fT4 concentrations when using a log-normal distribution, which could have important implications for the ultimate objective of this exercise (estimate the impact of perchlorate on lowering fT4 and subsequent effects on child neurodevelopment). I think that more thought needs to be given to the choice of fT4 distribution and its impact on results by conducting sensitivity analysis by running the models assuming a

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Specific Observations on Report (Volume 1) - *Jonathan Chevrier, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
		normal distribution of fT4. As I mentioned previously, the fact that a log-normal distribution may describe some published results raises concerns about the validity of the results given what is generally reported in terms of distribution.
5-2	Table 9	I was surprised that "thyroid" or "thyroid hormone" were not part of the search terms. I am also surprised that for some outcomes both T4 and thyroxine were used and for others, only thyroxine was used. I can't think of a reasonable rationale for this inconsistency. Also, restricting some search strings to the title may have resulted in missed articles (and using a different strategy for different strings is highly unusual). Although Google Search can list very large numbers of articles, PubMed generally generates a more reasonable number of hits when bollean terms are used (e.g. neurodevelopment AND hypothyroxinemia yielded 45 hits)
5-3	Last	I can see little justification for using only studies that found significant results between fT4 and neurodevelopment. Studies finding no significant results also have values if valid methods were used. Using only significant studies could overestimate the effect of perchlorate on fT4. If EPA believes that this method should be kept, the fact that the model may overestimate perchlorate's toxicity should be acknowledged.
5-4	Last bullet point	Small studies with significant results are generally believed to be more prone to publication bias – this is in fact what is evaluated when using funnel plot to estimate publication bias. Again, by eliminating studies with non-significant results and including small studies with significant results, the model's results may be affected by publication bias and overstate relationships. Also, was any information collected about the quality of the studies including potential for selection, information and/or confounding biases? Studies of poor quality (high risk of bias) should not be considered.
6-3	1	In the following sentence the units for fT4 should be indicated so that the coefficient can be understood.
6-4	Table 24	It is not clear how the confidence intervals were derived for these estimates. Was the uncertainty in deriving changes in fT4 due to perchlorate and changes in the outcome due to changes in fT4 considered? It seems to me that both of these should be reflected in the uncertainty of the prediction. Also, it makes little sense to me that the effect of perchlorate on reaction time would be stronger at the median of fT4 than at the 2.5th percentile. Would this be due to the assumed log-normal distribution of fT4?

ED_005043_00063236-00082

Specific Observations on Report (Volume 1) - *Jonathan Chevrier, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
6-6	Whole page	Here a linear regression was fit on the data representing the lower 50 percent of fT4. Essentially, EPA has decided that values in the higher percentile of fT4 should not influence the shape of the association in the lower 50 percent. EPA could have gone further by fitting a spline on the data, thereby neither forcing a quadratic relation over the range of fT4 but also not forcing a straight line below the 50th percentile of fT4. This method would also reduce the influence of outliers or other influential points on the beta coefficient (slope). Also, a note should indicate whether standard regression assumptions were verified (including the linearity assumption and evaluating the impact of influential points). In addition, I note that gestational age at blood sampling for fT4 measurement is not a confounder. This variable is not a causal determinant of IQ and thus, although a determinant of fT4, does not qualify as a confounder (such variables are termed instrumental variables). Also, BMI is a variable that is affected by thyroid hormones and as such not only does it not qualify as a confounder but could be a mediator of the fT4-IQ relation. Controlling for such a variable instrumental variables and mediators is considered to be over-control and can bias estimates of associations (most likely towards the null). Proper control for confounding could affect estimates in Table 26 and (properly) drive them away from the null and generate significant results for the multivariable model. Finally, the distribution of fT4 will not determine whether residuals from the linear regression are normally distributed (only the distribution of the outcome will). Therefore, the fact that fT4 was not normally distributed is no reason to log-transform this variable. Log-transforming fT4 assumes that the relation between fT4 and IQ is log-linear (i.e. multiplicative). Is there any reason to believe this? Does this function fit the data better than a linear-linear relation? Answers to these questions are important to ensure that predictions for changes in IQ are accurate and since EPA has the data on hand, they are able to answer them. I also note that the Pop et al. and Vermiglio et al. studies assumed linear-linear relations with the PDI, which is inconsistent.
6-11	Table 30	Here again, I find it difficult to explain that effects of perchlorate on IQ would be stronger at the median and 10th percentile of fT4 than at the 2.5th percentile. Stronger effects should occur at lower fT4 levels and so results suggest problems with the model.

ED_005043_00063236-00083

Claude Emond, Ph.D.

No specific observations on the Report provided.

Dale Hattis, Ph.D.

No specific observations on the Report provided.

Angela M. Leung, M.D., M.Sc.

Specific Observations on Report (Volume 1) - *Angela M. Leung, M.D., M.Sc.*		
Page	**Paragraph**	**Comment or Question**
18	Footnote 2	Suggest inserting the word **serum** before each mention of FT4 and TSH, i.e. "serum FT4 values" and "serum TSH"
20	2	This should read: "TSH acts on the thyroid gland to stimulate **iodine uptake to result in decreased** thyroid hormone production."
21	2	Suggest that the text regarding suppressed TSH be separated in order to clarify that this does not result from increased serum TBG concentrations. The text would be clearer as follows: "For example, as the first trimester progresses, increases in beta human chorionic gonadotropin (beta-hCG)[4], estrogen, and thyroid binding protein result in a higher serum T4 concentrations, making more fT4 available to the developing fetus (Morreale de Escobar, Obregón, & del Rey, 2007). Serum TSH concentrations are also mildly suppressed due to the action of beta-hCG as a mild thyroid hormone stimulator."
22	1	It is unclear what the two processes are from the ensuing text following this sentence: "In the first trimester of pregnancy, this increased output of thyroid hormones is due to **two specific processes**."
23	2	The word "because" is repeated twice. Suggest: "Maternal fT4 is particularly important in the first trimester of pregnancy because the fetal brain is solely dependent upon T4 of maternal origin during this period (Zoeller & Rovet, 2004), **as** the fetal thyroid gland does not form and become mature until later in development."
23	3	It is unclear what time period this sentence refers to. I think the text is meant to read and should be changed to the following: "Historically, the most commonly observed thyroid conditions resulting from hypothyroidism **in pregnancy** have been goiter (i.e., enlarged thyroid gland) and congenital hypothyroidism."
23	3	Technically, the list refers to hypothyroidism rather than hypothyroxinemia, since the latter is relevant only during pregnancy. Suggest: "**Hypothyroidism** may result from iodine

ED_005043_00063236-00084

Specific Observations on Report (Volume 1) - *Angela M. Leung, M.D., M.Sc.*		
Page	**Paragraph**	**Comment or Question**
		insufficiency, genetic disorders, autoimmune thyroid disease, thyroid surgery, pituitary insufficiency, or environmental factors."
23	4	**Hashimoto's thyroiditis** does not necessarily cause subclinical hypothyroidism, but rather increases the risk of hypothyroidism, whether it be subclinical or overt hypothyroidism. (i.e. There is a difference between Hashimoto's thyroiditis and hypothyroidism resulting from Hashimoto's thyroiditis.) Suggest: "Hashimoto's disease increases the risk of hypothyroidism, including both subclinical and overt hypothyroidism. Subclinical hypothyroidism is defined by only elevated TSH concentrations, yet serum T3 and T4 concentrations remain within the population reference range, while overt hypothyroidism is defined by elevated serum TSH concentrations concurrent with decreased serum T3 and T4 concentrations."
23	4	The term "clinical hypothyroidism" is confusing and not a conventional medical diagnosis. Suggest: "Subclinical hypothyroidism has the potential to progress to **overt hypothyroidism over time**, thus requires serum thyroid function test monitoring."
24	2	Suggest: "However, since the 2005 NRC report was published, several epidemiological studies have shown perchlorate exposure to be associated with changes in serum thyroid hormone levels (Blount et al., 2006; Steinmaus et al., 2013; Steinmaus et al., 2016) and Taylor et al. (2014), as well as an association between high maternal perchlorate exposure and risk of low IQ in offspring (Taylor et al. 2014)."
24	3	I think this should be hypothyroidism instead of hypothyroxinemia, as they are not interchangeable. Suggest: "Given the importance of a properly functioning thyroid for fetal and child growth (Forhead & Fowden, 2014), **hypothyroidism** may also be associated with abnormal fetal and child growth."
25	Figure 3	Now that hypothyroxinemia pathway has been added, the hypothyroidism box can be confusing. Hypothyroidism in the black box is meant to denote a situation of increased serum TSH and decreased serum T4/T3 concentrations (i.e. both must be met), whereas the blue hypothyroxinemia box denotes a situation of isolated serum T4 concentrations (technically this does not include T3) in the setting of **normal** serum TSH concentrations. Thus, suggest clarifying with subnotes in each of the hypothyroxinemia and hypothyroidism boxes to indicate the direction of serum T4/T3, T4, and TSH concentrations.
26	1	The word "overt" would clarify the intent of this sentence. Suggest: "Even without the presence of perchlorate as a thyroid disruptor, it is likely that the population is already exposed to a range of thyroid-affecting substances that may result in **overt** hypothyroidism

ED_005043_00063236-00085

Specific Observations on Report (Volume 1) - *Angela M. Leung, M.D., M.Sc.*		
Page	**Paragraph**	**Comment or Question**
		(elevated TSH, low fT4), subclinical hypothyroidism (elevated TSH, normal fT4), or hypothyroxinemia (normal TSH, low fT4) that will effectively be worsened by exposure to further endocrine disruption caused by perchlorate."
27	2	Consider inserting text to clarify that perchlorate has an approximate 30-fold relative higher potency than iodide to be taken up by thyroidal NIS. PMID 15650353.
28	1	Serum TBG concentrations approximately double (rather than decrease) during the first trimester and remain elevated until the end of gestation, thus this sentence appears to be incorrect. "…increases in hCG result in a higher production of T4 and reduced TSH **and TBG** (Morreale de Escobar et al., 2007)."
32	Figure 4	Suggest either "urine" or "urinary excretion" to maintain consistency throughout.
56	3	Regarding the "Iodine intake data for the study population" bullet, it would also be informative to know the number of subjects the urinary iodine measurements were obtained in. A study sample of >125 individuals is considered reliable when interpreting population urine iodine concentrations measured from a spot urine sample. Small study samples may not be accurate to form conclusions for population iodine status. The size of the study population is addressed in a later bullet, but for different reasons.
95	Table 2	It would be easier to read the table if it was split into the 5 studies for which further analysis was performed for the MCLG derivation and the 10 studies that were not further analyzed.
134	2	Presents an alternative population-based…
140	2	In addition, **subclinical hypothyroidism** (when the serum TSH is elevated but serum T3 and T4 levels remain normal) has been similarly associated with other cardiovascular risk factors, including diastolic hypertension, weight gain, insulin resistance, as well as congestive heart failure and mortality. A brief discussion can be inserted regarding this, which is different from hypothyroidism (inferred as overt hypothyroidism) reviewed in this section. Here are some references regarding adverse cardiovascular outcomes associated with subclinical hypothyroidism: 1. Andersen MN, Olsen AM, Madsen JC, et al. Levothyroxine Substitution in Patients with Subclinical Hypothyroidism and the Risk of Myocardial Infarction and Mortality. *PLoS One.* 2015;10(6):e0129793. 2. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med.* 2005;165(21):2460-2466. 3. Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual

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Specific Observations on Report (Volume 1) - *Angela M. Leung, M.D., M.Sc.*		
Page	**Paragraph**	**Comment or Question**
		participant data analysis from 6 prospective cohorts. *Circulation.* 2012;126(9):1040-1049. 4. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA.* 2010;304(12):1365-1374. 5. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM. Subclinical hypothyroidism and survival: the effects of heart failure and race. *J Clin Endocrinol Metab.* 2013;98(6):2326-2336. 6. Collet TH, Bauer DC, Cappola AR, et al. Thyroid Antibody Status, Subclinical Hypothyroidism, and the Risk of Coronary Heart Disease: An Individual Participant Data Analysis. *The Journal of clinical endocrinology and metabolism.* 2014:jc20141250. 7. Tseng FY, Lin WY, Lin CC, et al. Subclinical hypothyroidism is associated with increased risk for all-cause and cardiovascular mortality in adults. *J Am Coll Cardiol.* 2012;60(8):730-737.

Stephen M. Roberts, Ph.D.

No specific observations on the Report provided.

Joanne F. Rovet, Ph.D.

Specific Observations on Report (Volume 1) - *Joanne F. Rovet, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
X	3	Line 2: "they" referring to wrong referent
X	3	Line 4: "occurs and that allows for
X	3	Line 6: "establishes"
Xi	6	Start with "further" or similar link
	7	Start with "Second"
1-1	2	Maybe include idea of airbags
1-3	2	Change "which" to "that"
2-1	2	Second last line: change "could" to "can"
	4	Start with "The"
		Line 1: perhaps move "largely" to after "act"
2-3	1	Line 2: add "in order" before "to provide"
	1	Line 6: maybe define or introduce hCG if this is the first time mentioned
2-4	3	Line 3: "their respective reference ranges"
2-5	2	Line 8: comma after "published"

ED_005043_00063236-00087

Specific Observations on Report (Volume 1) - *Joanne F. Rovet, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
2-5	2	Line 10: 2016). Furthermore, Taylor…
2-8	3	Section 2.6: add more recent paper
	4	I would expand this paragraph
	6	Add more recent articles
3-3	1	Fourth last line: what's the reference for "it"
3-5	1	Line 3: add a reference after "data"
	2	Third last line "stimulating"
3-9	1	Line starting "In contrast": found this hard to read
3-13	1	Line starting "The similarity" : not sure of these assumptions
3-16	2	Middle paragraph "his/her": weren't all of Greer's subjects male?
		Third last line "perchlorate; they demonstrate" (data are plural)
4-2		Not sure what "Distances" mean in Table 4 heading
5-3	5.2.3	Line 3: That is, the studies that were identified found"
5-23	1	Mosaics and Categories need to be capitalized (by convention) as these are names of scales. Please do so throughout the report
5-25	1	Lines 2, 3, 5: "nonverbal cognitive delay"
5-25	1	Child ?nonverbal IQ
6-5		Table title: should this read Nonverbal IQ?
6-9	1	Line 5 "Excel, we estimated effects based on" – poor grammar
9-1		Table 39: I don't understand why differences in dose-unit changes are so great – perhaps an explanation somewhere

DRAFT

ED_005043_00063236-00088

VI. SPECIFIC OBSERVATIONS ON BBDR MODEL (VOLUME 2)

Hugh A. Barton, Ph.D.

Specific Observations on BBDR Model (Volume 2) - *Hugh A. Barton, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
A-5	1	"GA"?
A-7	Sec 2.2	"blood plasma" "arterial blood" Is it blood flow or plasma flow? Clarify.
A-50	2	Change "can" to "scan"
A-54	5	Change "for iodide for perchlorate" to "for iodide and perchlorate"
A-71	2	Difficult to follow this paragraph ("The data sets…")
A-84	2	"However, when pREG…" is an incomplete sentence

Nancy Carrasco, M.D., M.S.

No specific observations on BBDR Model provided.

Jonathan Chevrier, Ph.D.

No specific observations on BBDR Model provided.

Claude Emond, Ph.D.

Specific Observations on BBDR Model (Volume 2) - *Claude Emond, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
A7 (or 13 on pdf)	Middle of page	RNISthy_x = VmaxNIS_thy_x*CthyB_x/[CthyB_x + KmNIS_x*(1 + CthyB_y/KmNIS_y)]. Some terms are not described below the equation.
A8 (or14 on pdf)	Paragraph in the middle	It is important to note that EPA did corrections from preceding version(s) of the model. This is another reason to site the quality of the toxicologist who did the codes for this model.

Dale Hattis, Ph.D.

No specific observations on BBDR Model provided.

Angela M. Leung, M.D., M.Sc.

No specific observations on BBDR Model provided.

ED_005043_00063236-00089

Stephen M. Roberts, Ph.D.

No specific observations on BBDR Model provided.

Joanne F. Rovet, Ph.D.

No specific observations on BBDR Model provided.

DRAFT

ED_005043_00063236-00090

VII. SPECIFIC OBSERVATIONS ON APPENDICES B-G (VOLUME 3)

Hugh A. Barton, Ph.D.

No specific observations on Appendices B-G provided.

Nancy Carrasco, M.D., M.S.

No specific observations on Appendices B-G provided.

Jonathan Chevrier, Ph.D.

No specific observations on Appendices B-G provided.

Claude Emond, Ph.D.

No specific observations on Appendices B-G provided.

Dale Hattis, Ph.D.

No specific observations on Appendices B-G provided.

Angela M. Leung, M.D., M.Sc.

No specific observations on Appendices B-G provided.

Stephen M. Roberts, Ph.D.

No specific observations on Appendices B-G provided.

Joanne F. Rovet, Ph.D.

Specific Observations on Appendices B-G (Volume 3) - *Joanne F. Rovet, Ph.D.*		
Page	**Paragraph**	**Comment or Question**
E-3	2	Lines 5-7: don't make sense; need a verb
	3	General Cognitive Index
		Line 7: Perceptual needs to be capitalize but scales isn't called - manipulative
		Line 9: Memory; Line 10: Verbal, Numerical; Line 11 Motor – take out skills or scales

ED_005043_00063236-00091

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 6/15/2020 9:38:03 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
Subject: FW: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Attachments: Perchlorate Action Memo 6-15-20 v1.docx; Transmittal Memo OW to OP 6-15-20.docx; Transmittal Memo JM to DR 6-15-20.docx

Note that I sent a follow up note asking her to change the deadline from 6/18 to 6/17.

From: Burneson, Eric
Sent: Monday, June 15, 2020 1:01 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Stephanie
Attached are the updated memos. Can you please review and transmit the revised to Jennifer.
Also please advise what other materials are needed beyond the OGC concurrence?
Eric

From: Flaharty, Stephanie
Sent: Monday, June 15, 2020 10:57 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

I am awaiting updated memos for review, thanks!

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, June 15, 2020 10:55 AM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Sam and Stephanie:
Can you please advise me of the status of the transmittal /Action memos. We expect OMB clearance today and will need to move this package forward.
Are you awaiting my review of what Stephanie sent on Friday or is there more work to put together the FR signature package?

From: Flaharty, Stephanie
Sent: Friday, June 12, 2020 8:24 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

From: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Sent: Thursday, June 11, 2020 5:13 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Cc: Aguirre, Janita <Aguirre.Janita@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>
Subject: Heads-up: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Importance: High

Steph: Please make sure that the program leads for Perchlorate Final Action start with these memos for the final action next week.

Sandy

From: Evalenko, Sandy
Sent: Thursday, May 21, 2020 4:46 PM
To: Nurse, Leanne <Nurse.Leanne@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>
Cc: Manibusan, Mary <manibusan.mary@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Subject: Action for OMB review: NPDWR: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review

Leanne: Here's the OMB Review package for the NPDWR: Perchlorate Final Action (SAN 5555; RIN 2040-AF28). Attached are the signed transmittal memo, draft Action memo, OGC concurrence, and the FRN for OMB review. If you have questions, please let us know.

Thanks,
Sandy

Sandy Evalenko
Water Policy Staff
Office of Water (4101M)
3226K WJC East
(202) 564-0264 telephone

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Thursday, May 21, 2020 4:22 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: FW: Charlotte - for review/signature - Perchlorate FRN to OP for Interagency Review
Importance: High

Hi! Here is the signed memo. Thanks for pulling it together for me, Charlotte

---

From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Thursday, May 21, 2020 3:10 PM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Ross, David P <ross.davidp@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>
Subject: Charlotte - for review/signature - Perchlorate FRN to OP for Interagency Review
Importance: High

Hi Charlotte,

Please see the electronic blue folder for the Notice of Final Action on Perchlorate to go to OP to be submitted to OMB for interagency review. I spoke with Dave and he has delegated package approval/transmittal memo signature to you. When you are ready to approve, please sign the transmittal memo (attachment 1). Please let me know if you find any edits to the memo or the package. Once signed, please send it back to me, and Sandy will move it to the next step.

- For attachment 1, your e-signature in PDF will look something like this:

SHARON HAMER Digitally signed by SHARON HAMER Date: 2020.03.12 17:21:45 -04'00'

Attachments

1. SIGN: Transmittal memo for your signature
2. Draft Perchlorate FRN to be sent to OMB
3. Draft Action Memo (will be kept in draft until time for final FRN signature).
4. OCG Concurrence emails – see below my signature block

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: **aguirre.janita@epa.gov**

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Thursday, May 21, 2020 12:04 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Request for Concurrence - Revised Perchlorate FRN

Sam,

Per our discussion, I have reviewed the redlined version of all of the changes to the FRN since the FAR version. I confirmed that all of OGC's comments on the FAR version have been sufficiently addressed – and only had a couple of minor additional edits – please see attached (my edits are marked with comment bubbles). With these edits, the FRN is ready to move forward. Thanks.

Pooja

Pooja S. Parikh
Attorney- Advisor
U.S. Environmental Protection Agency
Office of General Counsel, Water Law Office
Phone: 202 564-0839
Email: parikh.pooja@epa.gov

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Thursday, May 07, 2020 9:52 AM

To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Perchlorate FRN -- OGC concurs with comment

On behalf of the General Counsel, I am providing OGC's concurrence on the Federal Register Notice referenced in the email below, subject to the attached comments. I will be representing OGC at the FAR meeting. Please let me know if you have any questions or require additional information. Thank you.

Pooja

Pooja S. Parikh
Attorney- Advisor
U.S. Environmental Protection Agency
Office of General Counsel, Water Law Office
Phone: 202 564-0839
Email: parikh.pooja@epa.gov

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/30/2017 12:36:07 PM
To: Grevatt, Peter [Grevatt.Peter@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]
CC: Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Ruf, Christine [Ruf.Christine@epa.gov]
Subject: RE: Materials needed
Attachments: One_pager_Perchlorate in drinking water_fv_32217.doc

Peter: I am assuming that Sarah has not yet seen the one pager we sent up last week on perchlorate. I think this is the most succinct and current status of the action. Please let us know if a more extensive background paper is needed.

From: Grevatt, Peter
Sent: Thursday, March 30, 2017 8:20 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>
Subject: FW: Materials needed

FYI. Can you two connect and determine the best off-the-shelf product for us to send up?

From: Best-Wong, Benita
Sent: Thursday, March 30, 2017 7:46 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Cc: Ruf, Christine <Ruf.Christine@epa.gov>
Subject: Materials needed

Peter,
As a follow up from Mike's general with Sarah yesterday, she would like a background paper on perchlorate. I'm hoping that you have something already prepared that I can provide to her. I'm also copying Christine in case she has something already available.
Benita

Benita Best-Wong
Acting Deputy Assistant Administrator
Office of Water
US EPA
1200 Pennsylvania Avenue, NW
Washington, DC 20460
202-566-1159

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/30/2017 12:30:00 PM
To: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: FW: Materials needed
Attachments: One_pager_Perchlorate in drinking water_fv_32217.doc

Here is what the IO has

From: Gonzalez, Yvonne V.
Sent: Thursday, March 30, 2017 8:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: RE: Materials needed

Eric,

The one-pager prepared by your team might be useful.

Regards,
Yvonne-Veronica Gonzalez
Special Assistant (on detail)
Office of Ground and Drinking Water
U.S. Environmental Protection Agency
(202)564-2912

From: Grevatt, Peter
Sent: Thursday, March 30, 2017 8:20 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>
Subject: FW: Materials needed

FYI. Can you two connect and determine the best off-the-shelf product for us to send up?

From: Best-Wong, Benita
Sent: Thursday, March 30, 2017 7:46 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Cc: Ruf, Christine <Ruf.Christine@epa.gov>
Subject: Materials needed

Peter,
As a follow up from Mike's general with Sarah yesterday, she would like a background paper on perchlorate. I'm hoping that you have something already prepared that I can provide to her. I'm also copying Christine in case she has something already available.
Benita

Benita Best-Wong
Acting Deputy Assistant Administrator
Office of Water
US EPA
1200 Pennsylvania Avenue, NW

Washington, DC 20460
202-566-1159

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 6/1/2020 6:23:43 PM
To: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: FW: FOR REVIEW: draft perchlorate response to comment document
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-19-20 v2.docx

Crystal and Lisa;
Jennifer spoke with me today about her comments on the perchlorate response to comment document. She has reviewed the Chapters 1-7 and is in the midst of reviewing Chapter 8. She stated that the responses in Chapters 1-7 are well written.
She is concerned that Chapter 8 contains some redundant responses in which the same issues are addressed. She asked that someone review chapter 8 responses with an eye toward reducing redundant responses and assuring that we don't have inconsistent language contained where we do have redundant responses. Crystal since you were able to do that effectively for Lead Free, I would like your help in doing that in Chapter 8 of the attached document.

Please note that

1. Jennifer is continuing with her review and will forward the document to Charlotte B with the understanding we can make combine changes that Crystal makes with any changes that result from Jennifer and Charlotte's review.
2. Jennifer prefers the Lead Free approach to summary responses for each section. She does not want us to change what we have done for perchlorate but when we prepare the LCR response to comment document she wants it to look more like the Lead Free document than the perchlorate document.

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, May 19, 2020 6:41 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FOR REVIEW: draft perchlorate response to comment document

DRAFT/DELIBERATIVE
Hello Jennifer,
Attached for your is the draft perchlorate response to comment document. Please let us know if you have questions or concerns.
Thanks,
Lisa

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/20/2020 1:17:33 PM
To: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
CC: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
Subject: FW: Important: Perchlorate submittal to OW
Attachments: Perchlorate Action Memo 5-19-20.docx; Draft Perchlorate Final Action FRN 5-19-20 v1.docx; Final Perchlorate Action for 12866 Review Transmittal Memo OGWDW to OW 5-19-20.pdf; 12866docketguidelines-09-27-10.pdf

Importance: High

FYI

From: Burneson, Eric
Sent: Wednesday, May 20, 2020 9:08 AM
To: Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Subject: FW: Important: Perchlorate submittal to OW
Importance: High

Macara: I understand that WPS are not processing the perchlorate action which is subject to a consent decree deadline because of missing items in the package related to FAR. Since WPS ran the FAR I don't see why this information cannot be added by WPS (note that there is no economic analysis for this final action). It is critical that this action be transmitted to OP ASAP. Thanks for your assistance.

From: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Sent: Wednesday, May 20, 2020 7:38 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: Important: Perchlorate submittal to OW
Importance: High

Good Morning,

There's some confusion in OW over our submittal of the perchlorate docs. for Charlotte's review. Joe asked that I enter the attached documents into CMS (w/o review) for Charlotte. Is this the formal submittal? To initiate OMB Review, we need to follow the Action Development Process checklist (as applicable) and label the FRN per the attached guidance. (Note: submit the FAR memo and associated concurrences in on PDF file.)

Thanks for your timely attention...any questions, please let me know, thanks!

OMB REVIEW OF RULE
Left Side ***Right Side***

□ OGC Concurrence e-mail (or letter) □ Core Workgroup concurrences: emails: ORD, OPEI , OECA □ FAR memo and attached Workgroup FAR concurrences □ Draft Economic Analysis (1 + e copy) * □ Note: Docket Guidelines https://intranet.epa.gov/actiondp/documents/12866docketguidelines-09-27-10.pdf	□ Transmittal Memo from DD to OD □ Transmittal Memo from OD to AA (Orig + yellow) □ Transmittal Memo from AA to OPEI (Orig + yellow) □ Draft Action Memo from AA to Administrator □ Draft Rule and Preamble FRN □Send all Files electronically to IO (SF) – will forward to OP https://intranet.epa.gov/actiondp/adp-templates/index.htm#adp

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/20/2020 1:07:43 PM
To: Lousberg, Macara [Lousberg.Macara@epa.gov]
CC: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
Subject: FW: Important: Perchlorate submittal to OW
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To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: Important: Perchlorate submittal to OW
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OMB REVIEW OF RULE

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Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/22/2017 9:19:38 PM
To: Messier, Dawn [Messier.Dawn@epa.gov]; Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: RE: Perchlorate peer review report
Attachments: 1 pager perchlorate in drinking waterV3.doc

Thanks Dawn:
I believe the attached addresses Dawns comments and incorporates her suggested edits.

Yvonne
Can you share with Peter for transmission to Mike.

From: Messier, Dawn
Sent: Wednesday, March 22, 2017 3:05 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: RE: Perchlorate peer review report

A few comments. Thanks! Dawn

Dawn Messier
U.S.E.P.A.
Office of General Counsel
Water Law Office
202-564-5517

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 1:56 PM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: RE: Perchlorate peer review report

Yvonne; Please see the draft note to Mike about perchlorate peer review. Also please find attached a draft one pager for the A.O. describing our activities. Please note the attached is still under review by OGC but I am sending to you and copying Dawn so that she can convey and comments/concerns to all once she has had a chance to review.

Mike:
Please find attached, a one page summary of our activities on perchlorate. The attached provides background information, identifies key issues and a timeline for moving forward. The attached highlights the recently completed peer review of the biologically based dose response (BBDR) model for perchlorate and the planned peer review of methodologies to develop alternative MCLGs using the BBDR model.

Please note that we recently received the final peer review report for the BBDR model. We plan to post this peer review document to our docket so that the public will be able to view the recommendations we have received for how to improve the BBDR model. The peer reviewers identified a number of areas for improvement or modification of the existing model for predicting thyroid hormone level changes caused by perchlorate exposure. The peer

reviewers recommended that the Agency develop a plan for further actions in order to maximize the benefit of any model revisions that are undertaken and to make decisions about priorities, timelines, and resources. Peer reviewers noted that models can always be improved, but the goal is to have a model that is fit for the intended purpose. The peer reviewers noted that the lack of a clear definition of that purpose for this model (i.e., how the model outputs would be used in developing the desired drinking water regulations) contributed to the difficulty they had in assessing whether the model was sufficiently good to apply.

We are working with our colleagues in ORD and FDA to implement many of the recommendations the peer reviewers made to the BBDR model. We believe that the purpose of the BBDR model will be more evident with the preparation of the MCLG Report that will describe alternative approaches for applying the BBDR model to develop potential perchlorate MCLGs. We hope to brief the Administrator's office on the perchlorate peer review process in April and intend to cover the recommendations from the first peer review and the draft MCLG report in April.

Please let us know if there is any more information you would like us to prepare in order inform the Administrator's office of these important activities.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 1:28 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Perchlorate peer review report

Eric,

Ann and I were on the same page. She thought an email note from Peter to Mike would suffice , including something on the findings and recommendations contained in the report.
I was just sending a heads up to Christina about the Desk Statement and holding it till we get an ok.

Can you or Lisa provide a draft of the email for Peter?

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 1:26 PM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate peer review report

I spoke with Jennifer about this and one idea we have is to mention posting the peer review report in the note that Ann/Mike will send to the A.O.
The draft one pager for perchlorate is under review by OGC since it references the Consent Decree.

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 11:56 AM
To: Gonzalez, Yvonne V. <Gonzalez.Yvonne@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate peer review report

I don't recall specifically mentioning placing the peer review report in the docket to Mike. We of course have spoken about conducting the peer review, we just did not get into the specifics of putting the report into the docket.

From: Gonzalez, Yvonne V.
Sent: Wednesday, March 22, 2017 11:48 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Perchlorate peer review report

Eric,
Jennifer and I do not recall teeing up (at the bi-weekly or LCR meetings) the Perchlorate peer review report and placing it in the docket to Mike. Do you or Lisa remember doing so? Anything Please advise. I don't want to hold anything up on the comms side, but I also know Ann is going to ask if we did.

DESK STATEMENT

To ensure the safety of drinking water for all Americans, EPA is continuing the regulatory process for perchlorate in drinking water. In response to recommendations from our Science Advisory Board, the agency is developing two new analyses to inform selection of a health based goal (the Maximum Contaminant Level Goal or MCLG) for the regulation. The first new analysis is the development of a biologically based dose response (BBDR) model and the second analysis is the development of methodologies to derive a MCLG for the regulation using the BBDR model. The agency held a peer review of the first of two new analyses to ensure the agency's perchlorate regulatory decision-making is based on the best available science. EPA has received the peer review report, is reviewing the recommendations and will be taking actions to improve the BBDR model as appropriate. EPA plans to conduct a second peer review of the second analyses describes methodologies for deriving a MCLG for using the BBDR model. To find a copy of the report please visit:
https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN 2040-AF28, significant

Purpose: To improve the health protection to drinking water consumers from perchlorate.

Background: On February 11, 2011, EPA announced its decision to regulate perchlorate based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant. SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013) and finalize the regulations 18 months after proposal (can extend up to 9 months).

Stakeholder Involvement: EPA consulted with the National Drinking Water Advisory Council in 2012 on potential requirements of the perchlorate regulation. EPA has also met or corresponded with industry groups including the Perchlorate Study Group, American Chemistry Council, the American Water Works Association and the U.S. Chamber of Commerce. EPA was sued by the Natural Resources Defense Council in 2016 for the Agency's failure to issue proposed and final regulations for perchlorate in accordance with SDWA timelines.

Key Issues/Internal Review: The key issue for perchlorate is establishing the Maximum Contaminant Level Goal (MCLG[1]) which is defined in SDWA as the "level at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety." In early 2012, the Agency sought recommendations from EPA's Science Advisory Board on how to derive a MCLG for perchlorate in accordance with SDWA. The SAB recommended that EPA derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based modeling. In response to SAB recommendations, FDA and EPA scientists worked to develop models to relate perchlorate exposure to biological effects to infants and other life stages. EPA completed an expert peer review of the models, and we are preparing for a second expert peer review of methodologies to apply the model to identify potential MCLGs for perchlorate. Once peer review of these analyses are completed, OW will brief the Administrator and seek input on at what level the MCLG should be set and whether the Agency should

Ex. 5 Attorney Client (AC)

Legal Deadlines: EPA is under a consent decree with enforceable dates of October 31, 2018 for signature of a proposed MCLG and NPDWR and a signature date of December 19, 2019 for the final MCLG and NPDWR for perchlorate.

Timing: In order to complete necessary analyses for development of a proposed rule, including the Heath Risk Reduction Cost Analysis required by SDWA, we will need to initiate expert peer review of the approaches to derive an MCLG in mid May and complete the review in October 2017. We would like to brief the A.O. about peer review in April.

---

[1] Maximum Contaminant Level Goal (MCLG) is a non-enforceable public health goal. The enforceable standard, the Maximum Contaminant Level (MCL) is set as close to the MCLG as feasible using best available treatment technology and taking cost into consideration.

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/22/2017 5:56:24 PM
To: Gonzalez, Yvonne V. [Gonzalez.Yvonne@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]
Subject: RE: Perchlorate peer review report
Attachments: 1 pager perchlorate in drinking water.doc

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Acting Special Assistant
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Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN 2040-AF28, significant

Purpose: To improve the health protection to drinking water consumers from perchlorate.

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Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/22/2017 3:57:23 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]
Subject: RE: Notes on LCR and Perchlorate
Attachments: 1 pager perchlorate in drinking water.doc

Lisa I have revised the one pager for perchlorate. Since we are mentioning the consent decree I want OGC input before we send this up. Carrie or Dawn can you please take a quick look at the attached which is for the A.O. as a heads up.

From: Christ, Lisa
Sent: Wednesday, March 22, 2017 10:49 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Notes on LCR and Perchlorate

Here's the perchlorate 1 pager...

From: Burneson, Eric
Sent: Wednesday, March 22, 2017 10:25 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notes on LCR and Perchlorate

Here is a draft of the LCR one pager. Take a look to confirm its accuracy and use as a model for your perchlorate paper.

From: Christ, Lisa
Sent: Tuesday, March 21, 2017 5:20 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Notes on LCR and Perchlorate

Here are the schedules -

From: Gonzalez, Yvonne V.
Sent: Tuesday, March 21, 2017 3:16 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Notes on LCR and Perchlorate

Eric and Lisa,

Ann's looking to get a couple of notes (one-pager) on the LCR and Perchlorate schedules Mike could send to the political team ahead of scheduling meetings? I know we have an LCR revisions weekly coming up – but can we turn something around to them as soon as possible? I believe the OW weeklies on the LCR nominations have triggered some folks. Please advise.

Thanks,
Yvonne-Veronica Gonzalez
Acting Special Assistant
Office of Ground and Drinking Water
(202)564-2912

Action Information

Action Title: National Primary Drinking Water Regulation for Perchlorate, Tier 1, SAN 2040-AF28, significant

Purpose: To improve the health protection to drinking water consumers from perchlorate.

Background: On February 11, 2011, EPA announced its decision to regulate perchlorate based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant. SDWA requires that EPA propose a drinking water regulation within 24 months of a determination to regulate a contaminant (February, 2013) and finalize the regulations 18 months after proposal (can extend up to 9 months).

Stakeholder Involvement: EPA consulted with the National Drinking Water Advisory Council in 2012 on potential requirements of the perchlorate regulation. EPA has also met or corresponded with industry groups including the Perchlorate Study Group, American Chemistry Council, the American Water Works Association and the U.S. Chamber of Commerce. EPA was sued by Natural Resource Defense Council in 2016 for the Agency's failure to issue proposed and final regulation for perchlorate in accordance with SDWA timelines.

Key Issues/Internal Review: The key issue for perchlorate is establishing the Maximum Contaminant Level Goal (MCLG[1]) which is defined in SDWA as the "level at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety." In early 2012, EPA sought recommendations from the Science Advisory Board on how to derive a MCLG for perchlorate in accordance with SDWA. The SAB recommended that EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling." In response to SAB recommendations, FDA and EPA scientists worked to develop models to relate perchlorate exposure to biological effects to infants, and other life stages. EPA completed an expert peer review of the models, and we are preparing for a another expert peer review of methodologies to apply the model to identify potential MCLGs for perchlorate. Once peer review of these analyses are completed OW will brief the Administrator and seek input on what level the MCLG should be set and

Ex. 5 Attorney Client (AC)

Legal Deadlines: EPA is under a consent decree with a enforceable dates of October 31, 2018 for signature of a proposed action and a signature date of December 19, 209 for the finale action.

Timing: In order to complete necessary analyses for development of a proposed rule, including the Heath Risk Reduction Cost Analysis required by SDWA, we will need to initiate expert peer review of the approaches to derive an MCLG in mid May and complete the review in October 2017. We would like to brief the A.O. about peer review in April.

---

[1] Maximum Contaminant Level Goal (MCLG) is a non-enforceable public health goal. The enforceable standard, the Maximum Contaminant Level (MCL) The MCL is set as close to the MCLG as feasible taking cost into consideration.

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/19/2020 2:35:29 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
BCC: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
Subject: RE: Notice of Final Action on Perchlorate
Attachments: Perchlorate Action Memo 5-19-20.docx; Draft Perchlorate Final Action FRN 5-19-20 v1.docx; Transmittal Memo JM to DR 5-18-20.docx

Attached is a clean version of the notice with your edits accepted. Also attached is a clean version of the Action memo with the edits I sent you last night accepted. Lastly attached is the unchanged memo from you to Dave Ross.

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Tuesday, May 19, 2020 9:15 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Eric – I have made two minor edits in the attached. I will send this to Charlotte so that she can see how we've addressed her comments. At the same time we will submit formally to OW. Please send us the final clean versions of the memos and the action for that process.

Thanks much
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 8:42 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

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Subject: FW: Notice of Final Action on Perchlorate

Eric – please let me know if you want to discuss.

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Monday, May 18, 2020 5:29 PM
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Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

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From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Monday, May 18, 2020 3:01 PM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Charlotte – as agreed, I'm sending you the draft final perchlorate FRN for review. The redline includes the changes made since the FAR. I'm also including the draft Action Memo. Please let us know if your preference is to have these submitted to OW through CMS now or after you have reviewed. Let me know if you want to talk.

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Subject: FW: Notice of Final Action on Perchlorate

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Attached for transmission to OW are revised versions of the FRN for the Perchlorate Final Action. There is both a clean and track changes version that includes edits made since initiating FAR (including the edits you asked for on Saturday and adding 3 more SAB recommendations to page 14 that were in the proposal but were not included in the draft we provided you on Friday). Also please find clean version of the transmittal memo from you to Dave Ross and the Action memo incorporating your edits.

Please note that there is also a redline version of the Action Memo for you to see the responses to your comments on the document. I do not recommend transmitting that memo to OW.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

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Sent: Monday, May 18, 2020 2:18 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
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Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Attached are the revised Redline and Clean versions of the Perchlorate FR Notice. Once we are ready for OP's submittal to OMB let me know and I will provide a version that adheres to OP's file name formatting guidelines.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 1:14 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Sam

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2. Provide the same level of detail on the SAB recommendations as was included in the proposal.
3. I don't think the HRRCA text is necessary and do not want to add it at this stage since there are OGC edits that already make this clear.

Eric

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
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To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
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Thanks for your work on this.
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Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

I recommend that you approve and transmit the attached notice to the Office of Water for their review, approval and transmission to the Office of Policy to initiate interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

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Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
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Message

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Sent: 10/6/2017 8:03:40 PM
To: Wadlington, Christina [Wadlington.Christina@epa.gov]
CC: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: RE: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

I have also sent a notice to our Federal Partners.

From: Wadlington, Christina
Sent: Friday, October 06, 2017 3:52 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: Re: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

Thanks Eric!

I'll let comms know that external folks are now aware.

Sent from my iPhone

On Oct 6, 2017, at 3:28 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

> I just spoke with three of the people requesting extensions of the deadlines:
> AWWA – Kevin Morely
> Perchlorate Study Group - Tom Roberts
> Chlorine Institute – Erica Bernstein
>
> I left a message with
> American Chemistry Council – Mark Gibson
>
> And I left a message with
> NRDC – Erik Olson explaining that we would be extending the deadline(after consulting with Carrie Wehling).
>
> ---
>
> **From:** Wadlington, Christina
> **Sent:** Friday, October 06, 2017 3:02 PM
> **To:** Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
> **Cc:** Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
> **Subject:** RE: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

Did SRMD want to touch base with OGC or did you want me to? Happy with either.

From: Flaharty, Stephanie
Sent: Friday, October 06, 2017 2:57 PM
To: Wadlington, Christina <Wadlington.Christina@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Proceed with roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material
Importance: High

Thanks !

From: Wadlington, Christina
Sent: Friday, October 06, 2017 2:55 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Question on roll out -- Perchlorate - Extension of comment Period FRN for Peer Review Material

Afternoon,

Please find an updated roll out. We can start the notifications asap.

**

RELEASE SCHEDULE
October 6, 2017

- SRMD informally notifies requestors via phone call (Eric)
- OGC notifies NRDC (via phone call) (Dawn)
- OGWDW/SRMD notification of Regional Contacts (Christina/Lisa)
- SRMD notification of federal partners (FDA, ATSDR, NIEHS, OMB)
- OPA notification of Regional PADS and federal agencies' (OW comms)

Release Day (when publically available on FR site; public inspection day)

8:00 a.m	OGWDW stakeholder heads up (Peter/Jennifer emails)
10:00 a.m	OCIR Congressional heads up emails (Matt)
11:00 p.m	Website goes live (Russ/Christina)
	Broader congressional notifications (emails with link to website) (OW Comms)

**** Send formal notification letters to requestors once available**

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/18/2020 6:47:55 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
Subject: FW: Notice of Final Action on Perchlorate
Attachments: Draft Perchlorate Final Action FRN 5-18-20 v1 Redline.docx; Draft Perchlorate Final Action FRN 5-18-20 v1 Clean.docx; Perchlorate Action Memo 5-18-20.docx; Perchlorate Action Memo 5-18-20redline.docx; Transmittal Memo JM to DR 5-18-20.docx

Jennifer:

Attached for transmission to OW are revised versions of the FRN for the Perchlorate Final Action. There is both a clean and track changes version that includes edits made since initiating FAR (including the edits you asked for on Saturday and adding 3 more SAB recommendations to page 14 that were in the proposal but were not included in the draft we provided you on Friday). Also please find clean version of the transmittal memo from you to Dave Ross and the Action memo incorporating your edits.

Please note that there is also a redline version of the Action Memo for you to see the responses to your comments on the document. I do not recommend transmitting that memo to OW.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, May 18, 2020 2:18 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Attached are the revised Redline and Clean versions of the Perchlorate FR Notice. Once we are ready for OP's submittal to OMB let me know and I will provide a version that adheres to OP's file name formatting guidelines.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 1:14 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Sam

1. Change the title please. This was requested by OGC at Sr. Leadership levels.
2. Provide the same level of detail on the SAB recommendations as was included in the proposal.
3. I don't think the HRRCA text is necessary and do not want to add it at this stage since there are OGC edits that already make this clear.

Eric

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, May 18, 2020 12:41 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Here is a revised Redline of the document (from FAR). We had a few questions/issues for your consideration about the attached file. Specifically:,

1- Page #1, Notice Tittle: We did not accept the edits to the notice tittle. Because, the tittle of the notice was specifically crafted by OGC to capture the multiple actions EPA is taking. Suggest consulting with OGC before modifying this tittle.
2- Page #14, SAB Recommendations: SAB provided 4 main recommendations in 2013 but we only listed the first recommendation. Please advise if we should list all 4 recommendations here or not.
3- Page #26, Missing HRRCA Text: This language was offered by TAB in its 5-13-20 version of the draft FRN, but it did not show up in the version provided by OGWDW with Eric's & Jennifer's comments. We have inserted the language here for the reviewer's consideration. Please advise if we should keep it.

Once you provide your feedback, I will modify the redline version and also provide a Clean copy for transmittal.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 8:42 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting

<Guilaran.Yu-Ting@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Lisa and Sam
Attached are Jennifer's comments and edits on the draft FRN. I have responded to her questions in the attached and made some additional edits. Can you please get a revised clean version and another redline version that compares this document and the version that was distributed to FAR?
Thanks for your work on this.
Eric

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Saturday, May 16, 2020 11:39 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Looks very good. See p. 6 for my only concern w/the revisions.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 15, 2020 5:03 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: Notice of Final Action on Perchlorate

Jennifer

Attached for your approval and transmittal to the Office of Water for their approval and transmittal to the Office Policy for initiation of interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate." Also attached for your review are a draft transmittal memo from you to the Assistant Administrator of Water, a draft Action Memorandum and a track changes version of the FR notice that denotes the changes made as a result of Final Agency Review.

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

I recommend that you approve and transmit the attached notice to the Office of Water for their review, approval and transmission to the Office of Policy to initiate interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/13/2020 9:27:47 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: Revised Perchlorate Briefing Documents
Attachments: Decision for Perchlorate Final Regulatory Action_3-13-20_revised. .docx; Perchlorate Recommendations for PWS 3-13-2020.docx; Perchlorate Reductions 3-13-2020.docx

Jennifer:
Attached please find a revised Perchlorate Briefing documents. We had submitted a previous versions of these document for OW review along with the Perchlorate Reductions and Recommendations Documents. We have updated these documents while awaiting further comments from OW. The revisions made to the documents are as follows

- The one pager – Decision for Perchlorate Final Regulatory Action – Has been updated in response to Dave's request to incorporate information about the timing of the release of the stipulation to NRDC regarding the consent decree. This document reflects OGC's input.
- The Reductions Document – has been updated to reflect the information we received from the States of Maryland and Ohio regarding the status of the system that previously detected perchlorate at levels greater than 18ppb. We have also added a document number.
- The Recommendations Document has been updated to reflect add a Document Number.

If OW has not yet reviewed the last versions provided we recommend sending these forward to replace the versions awaiting review. If there are comments on the previous versions we can incorporate those prior to sending them forward.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/17/2020 1:30:06 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents
Attachments: Perchlorate Recommendations for PWS_03.17.2020.Changes.docx; Perchlorate Reductions_03.17.2020RLSO.docx

Lisa: I have made additional edits to the documents attached to further expand the introduction to the Reductions Document and to address the POU text by describing the option as a Point of Use or Point of Entry Treatment option. Can you/Sam prepare clean versions of these documents so that we are ready for the 10:00 deadline.

Joe, Yu Ting and Jennifer
I am assuming Dave needs to see the mark ups to verify the edits so I am copying you in case you want to review while we are preparing clean versions.
Eric

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, March 17, 2020 8:16 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric, please see the revised document attached. I noticed we were missing references we added on 2/28 so I put those back in the reductions document. I do not agree with a edit on page 2 (highlighted blue) stating POU protects the whole home. Let us know if you'd like additional changes.

Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 4:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Thanks. Can I get a revised by 8:30 am tomorrow morning?

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, March 16, 2020 3:42 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents

Eric,
I think they are mostly straight forward. If I recall we were asked previously for underlying data for the AZ and NV surface water data, I don't think we have it, but Sam is checking. The questions about storage for hypochlorite should be in the AWWA protocol. Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, March 16, 2020 3:02 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

Lisa:
Please take a look at the comments/ revisions in the attached and let me know if you would like to have a call to discuss how to incorporate these changes.
Eric

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Monday, March 16, 2020 2:53 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: EDITS - RE: Revised Perchlorate Briefing Documents

From: Aguirre, Janita <Aguirre.Janita@epa.gov>
Sent: Monday, March 16, 2020 2:49 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: EDITS - RE: Revised Perchlorate Briefing Documents
Importance: High

Hi Jennifer,

A few edits from Dave. Please review and confirm. In particular, please address the comment bubbles in the "Perchlorate Reductions" document. Please also review the write-up under #4 in the "Perchlorate Recommendations for PWS" document to confirm that it uses guidance type language, rather than authoritative, regulatory language. Due to formatting, yellow highlights (rather than redline) show changed text.

This is due tomorrow by noon, so please let me know as soon as the edits are incorporated.

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: **aguirre.janita@epa.gov**

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Friday, March 13, 2020 5:34 PM
To: Aguirre, Janita <Aguirre.Janita@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate Briefing Documents

Janita – your assistance on this is appreciated! Is it possible to provide these revised documents – updated per Dave's input?

Thank you
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, March 13, 2020 5:28 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Perchlorate Briefing Documents

Jennifer:
Attached please find a revised Perchlorate Briefing documents. We had submitted a previous versions of these document for OW review along with the Perchlorate Reductions and Recommendations Documents. We have updated these documents while awaiting further comments from OW. The revisions made to the documents are as follows

- The one pager – Decision for Perchlorate Final Regulatory Action – Has been updated in response to Dave's request to incorporate information about the timing of the release of the stipulation to NRDC regarding the consent decree. This document reflects OGC's input.
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- The Recommendations Document has been updated to reflect add a Document Number.

If OW has not yet reviewed the last versions provided we recommend sending these forward to replace the versions awaiting review. If there are comments on the previous versions we can incorporate those prior to sending them forward.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/17/2020 2:05:43 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]
CC: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents - no later than 10am tomorrow
Attachments: Perchlorate Recommendations for PWS_03.17.2020.CleanV.docx; Perchlorate Reductions_03.17.2020 CleanV.docx; Perchlorate Recommendations for PWS_03.17.2020.Changes.docx; Perchlorate Reductions_03.17.2020RLSO.docx; Decision for Perchlorate Final Regulatory Action_3-13-20_revisedOWIO.docx; Option Selection for Perchlorate_final_01.09.2020.pdf

Janita:
I am sending a reply because Joe is experiencing some email difficulties. Attached are clean and track changes versions of the recommendations and reductions documents that reflect edits and comments from Dave. Please note that in some cases we were not able to obtain additional data from the studies
Also attached are the 2 briefing documents that are not changed by Dave's review

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Monday, March 16, 2020 9:49 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: Fwd: EDITS - RE: Revised Perchlorate Briefing Documents - no later than 10am tomorrow

FYI

Joe
(202) 564-0340

Begin forwarded message:

> **From:** "Aguirre, Janita" <Aguirre.Janita@epa.gov>
> **Date:** March 16, 2020 at 8:11:02 PM EDT
> **To:** "McLain, Jennifer L." <Mclain.Jennifer@epa.gov>
> **Cc:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>
> **Subject: RE: EDITS - RE: Revised Perchlorate Briefing Documents - no later than 10am tomorrow**
>
> Dave wants to review the updates, so please send no later than 10am tomorrow (Tuesday).
> That will give us time to flip and have Dave review/clear by noon Tuesday.
>
> Thank you,
> Janita
>
> **Janita Aguirre – Special Assistant to David Ross and Anna Wildeman**
> U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
> Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov
>
> **From:** Aguirre, Janita
> **Sent:** Monday, March 16, 2020 2:49 PM
> **To:** McLain, Jennifer L. <Mclain.Jennifer@epa.gov>

Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: EDITS - RE: Revised Perchlorate Briefing Documents
Importance: High

Hi Jennifer,

A few edits from Dave. Please review and confirm. In particular, please address the comment bubbles in the "Perchlorate Reductions" document. Please also review the write-up under #4 in the "Perchlorate Recommendations for PWS" document to confirm that it uses guidance type language, rather than authoritative, regulatory language. Due to formatting, yellow highlights (rather than redline) show changed text.

This is due tomorrow by noon, so please let me know as soon as the edits are incorporated.

Thank you,
Janita

Janita Aguirre – Special Assistant to David Ross and Anna Wildeman
U.S. Environmental Protection Agency | Office of Water | Office of the Assistant Administrator
Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Friday, March 13, 2020 5:34 PM
To: Aguirre, Janita <Aguirre.Janita@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate Briefing Documents

Janita – your assistance on this is appreciated! Is it possible to provide these revised documents – updated per Dave's input?

Thank you
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, March 13, 2020 5:28 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Perchlorate Briefing Documents

Jennifer:
Attached please find a revised Perchlorate Briefing documents. We had submitted a previous versions of these document for OW review along with the Perchlorate Reductions and Recommendations Documents. We have updated these documents while awaiting further comments from OW. The revisions made to the documents are as follows

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- The Reductions Document – has been updated to reflect the information we received from the States of Maryland and Ohio regarding the status of the system that previously detected perchlorate at levels greater than 18ppb. We have also added a document number.
- The Recommendations Document has been updated to reflect add a Document Number.

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Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/15/2020 9:03:15 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: Notice of Final Action on Perchlorate
Attachments: Draft Perchlorate Final Action FR Notice 5-15-20 v1 Redline (002).docx; Draft Perchlorate Final Action FR Notice 5-15-20 v1.docx; Perchlorate Action Memo 5-15-20.docx; Transmittal Memo JM to DR 5-15-20.docx

Jennifer

Attached for your approval and transmittal to the Office of Water for their approval and transmittal to the Office Policy for initiation of interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate." Also attached for your review are a draft transmittal memo from you to the Assistant Administrator of Water, a draft Action Memorandum and a track changes version of the FR notice that denotes the changes made as a result of Final Agency Review.

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

I recommend that you approve and transmit the attached notice to the Office of Water for their review, approval and transmission to the Office of Policy to initiate interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/28/2020 5:48:51 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]
BCC: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: Revised Document
Attachments: Perchlorate Reductions 2-28-20RLSO.docx; Perchlorate Recommendations for PWS 2-28-20 Clean.docx; Perchlorate Recommendations for PWS 2-28-20 RLSO.docx; Perchlorate Reductions 2-28-20clean.docx

Joe:
Attached please find clean and track changes versions of the perchlorate recommendations and reductions documents. We have addressed Charlotte's questions about the documents using the comment bubbles in the RLSO versions. I am also available for further discussion.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Friday, February 28, 2020 10:30 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: RE: Revised Document

Thank you Eric and Lisa!

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 28, 2020 10:26 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: RE: Revised Document

Thank you Lisa.
Joe : I will provide a revised version of the documents by 1:00.

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Friday, February 28, 2020 10:05 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: RE: Revised Document

Hi Joe,
I'm working on it now.

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Friday, February 28, 2020 9:48 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: RE: Revised Document

Lisa/Eric – Do we have a timing on when revised perchlorate documents addressing Charlotte's comments will be ready? OW is putting together materials for Dave's weekend review and they asked about the status.

Thanks!

From: Tiago, Joseph
Sent: Thursday, February 27, 2020 12:38 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Revised Document

Please find attached Charlotte's comments on the perchlorate documents. Thanks!

From: Tiago, Joseph
Sent: Wednesday, February 26, 2020 1:03 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Revised Document

Sent. Thanks!

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Wednesday, February 26, 2020 11:49 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Revised Document

Thank you all! These look great.

Joe – please send the attached versions forward to OW.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 26, 2020 8:21 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa

<Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: Attached please find clean copies of the recommendations and reductions documents for perchlorate. We have incorporated your edits. Please note with respect to your question about CCR reporting of perchlorate monitoring

CCR regulations under 141.153.(d)(1) requires the CCR include data on detected contaminants subject to mandatory monitoring including

i. Contaminants subject to an MCL, action level, MRDL or TT
ii. Contaminants for which monitoring is required under the UCMR
iii. Disinfection byproducts or micriobial contaminants for which monitoring is required.

Therefore if a system monitors for perchlorate outside of UCMR there is no requirement to report it on the CCR. If a system monitored for perchlorate in the UCMR 1 and detected it, then they were required to report it on the CCR for the next 5 years because 141.153(d)(3)(ii) UCMR results "need only be included in CCR for 5 years from the date of last sample or until any of the contaminants becomes regulated and subject to routine monitoring requirements, whichever comes first."
ASDWA is making arrangements for us to speak with the impacted States on Friday and or Monday morning.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Sunday, February 23, 2020 9:13 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Thank you Eric & Lisa – The attached contain a very few edits/comments. And then, these are ready to go to OW for review. Regarding the outreach plan, continue to pursue the discussions with ASDWA and AWWA as we discussed and agreed to with Dave. However, I'm not sure that we can say these reports will be released soon, maybe it is better to say that there is the potential for them to be issued in the near term.

Thanks much,
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 21, 2020 10:15 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Thursday, February 20, 2020 4:19 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Wednesday, February 12, 2020 11:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>

Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Appointment

From: Burneson, Eric [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2cacb9a8d49f49af80531e9e2ccb9018-eburneso]
Sent: 5/5/2020 3:51:07 PM
To: Lisa Christ [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]

Subject: Perchlorate Response to Comments
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-4-20.egb.docx
Location: Microsoft Teams Meeting

Start: 5/5/2020 6:00:00 PM
End: 5/5/2020 6:30:00 PM
Show Time As: Tentative

I would like to discuss the comments I have provided thus far on the perchlorate RTC document and provide an opportunity for you to ask any questions about comments to date.

Join Microsoft Teams Meeting

Ex. 6 Personal Privacy (PP)

Local numbers | Reset PIN | Learn more about Teams | Meeting options

---

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/4/2020 11:09:41 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Draft Perchlorate Response to Comment Document
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-4-20.egb.docx

Sam
Attached please find a copy of my comments on the response to comment document through section 6. I have not made any modifications to my comments on the previous sections.
Eric

From: Burneson, Eric
Sent: Friday, May 01, 2020 6:39 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Sam:
We may need to have this document cleared by OGC to submit the FRN to OMB, so its critical that we get them a version ASAP. I have provided my comments through section 5 on the attached. I will provide an updated version of this document as I complete more sections.
Eric

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, May 01, 2020 12:30 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

No. I was waiting to have a consolidated document ready for them before sending separate pieces of the document, so it would be easier for them to cross-reference the responses. Let me know if I should send this version to Pooja/Carrie for their concurrent review.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 01, 2020 12:25 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>

Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Thanks is their review of these other sections ongoing?

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, May 01, 2020 12:24 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Hi Eric,

OGC has reviewed only a few sections of this document (1, 5, & 9). They have not reviewed the health effects section (Section 8).

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 01, 2020 11:54 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Thanks Lisa and Sam. I am reviewing this document now. Can you remind me if OGC has cleared this version or if they are conducting a concurrent review?

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, April 29, 2020 12:19 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Draft Perchlorate Response to Comment Document

Hi Eric,
Please see the attached draft response to comment document for the perchlorate proposal. There are comment bubbles in this version, but you can review in "no markup" if you'd prefer. I've also attached a key I used as a cross reference comments since some responses point to others. This is in my short had so may not be as useful for you. Let us know if you have questions or concerns.
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, April 29, 2020 1:43 AM

To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Draft Perchlorate Response to Comment Document

Hi Lisa,

Attached is the draft Perchlorate RtC Document. I incorporated the final input provided by ORD. This version also includes annotated comments from reviewers. Let me know if we should also provide a clean copy for review at this stage.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/13/2020 8:24:42 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Subject: RE: FOR REVIEW: draft perchlorate action and transmittal memos
Attachments: Transmittal Memo JM to DR 5-13-20 v1.docx; Perchlorate Action Memo 5-13-2020 .docx

Lisa:
Attached please find my suggested edits to the Perchlorate transmittal memo and action memo. I modified the memos to reflect our status of submission to OMB for Interagency review.
I am copying Stephanie so that she may provide any additional edits to assure consistency with Agency templates.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, May 06, 2020 3:51 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FOR REVIEW: draft perchlorate action and transmittal memos

DRAFT DELIVERABLE
Hi Eric,
For you review are the draft memos to accompany the perchlorate final action. Please let us know if you have question, concerns or need more information.
Thanks,
Lisa

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/20/2020 9:18:59 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: RE: Revised Document
Attachments: Perchlorate Reduction Outreach Plan v2.docx; Perchlorate Recommendations for PWS_formatcw.v2.docx; Perchlorate Reductions 2-19-20 v1.docx

Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Wednesday, February 12, 2020 11:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
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To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Pre-Publication Outreach for Reductions of Perchlorate in Drinking Water: Status February 2020

To confirm and/or update the information on the 15 water systems that detected perchlorate > 18 ppb during UCMR1, TAB staff will coordinate with ASDWA and AWWA.

Working with Alan Roberson of ASDWA, TAB staff will conduct calls with the states of Florida, Georgia, Louisiana, Maryland, Mississippi, New Mexico, Nevada, Ohio, Oklahoma, Pennsylvania, Puerto Rico and Texas to:

- Provide notification that we will be highlighting publicly available data from UCMR1 in a perchlorate occurrence status report to be released soon.
- Share the information on water system's in their state we have obtained and check to see if there's additional information to add (monitoring, source water change, treatment installed, etc).

Working with Steve Via of AWWA, TAB staff will:

- Provide notification that we will be highlighting publicly available data from UCMR1 in a perchlorate occurrence status report to be released soon.
- Share the information on member water system's we have obtained and check to see if there's additional information to add(monitoring, source water change, treatment installed, etc).

Schedule:

Contact ASDWA and AWWA – February 24

Schedule calls with States – February 25

Complete calls & obtain AWWA data – February 26-27

Update document – February 28

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 11/26/2019 9:24:16 PM
To: Wendelowski, Karyn [wendelowski.karyn@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Behl, Betsy [Behl.Betsy@epa.gov]
Subject: RE: Perchlorate
Attachments: Option Selection for Perchlorate 11-21-19 v1 jlm.docx

Karyn:
The briefing has not happened nor is it scheduled. I have asked the team to assume that we will not brief the Administrator until mid December based upon input from OW – IO. Attached is a revised briefing from Jennifer McLain.

If you are in tomorrow it would be good to get your input on a few questions related to this briefing. Thanks

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Wendelowski, Karyn
Sent: Tuesday, November 26, 2019 1:33 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Albert, Ryan <Albert.Ryan@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Weisman, Richard <Weisman.Richard@epa.gov>
Subject: Perchlorate

Hi All: - DOJ has asked me to check in with you on where we are with respect to schedule and timing. Has a briefing occurred? Any decisions?

Thanks (and Happy Thanksgiving),

Karyn

Karyn Wendelowski
Attorney-Advisor
Water Law Office
Office of General Counsel
(202)564-5493

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/1/2020 10:38:44 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Draft Perchlorate Response to Comment Document
Attachments: Consolidated Perchlorate Draft Comment Response Document 5-1-20.egb.docx

Sam:
We may need to have this document cleared by OGC to submit the FRN to OMB, so its critical that we get them a version ASAP. I have provided my comments through section 5 on the attached. I will provide an updated version of this document as I complete more sections.
Eric

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, May 01, 2020 12:30 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

No. I was waiting to have a consolidated document ready for them before sending separate pieces of the document, so it would be easier for them to cross-reference the responses. Let me know if I should send this version to Pooja/Carrie for their concurrent review.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 01, 2020 12:25 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Thanks is their review of these other sections ongoing?

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, May 01, 2020 12:24 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Hi Eric,

OGC has reviewed only a few sections of this document (1, 5, & 9). They have not reviewed the health effects section (Section 8).

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 01, 2020 11:54 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Draft Perchlorate Response to Comment Document

Thanks Lisa and Sam. I am reviewing this document now. Can you remind me if OGC has cleared this version or if they are conducting a concurrent review?

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, April 29, 2020 12:19 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Draft Perchlorate Response to Comment Document

Hi Eric,
Please see the attached draft response to comment document for the perchlorate proposal. There are comment bubbles in this version, but you can review in "no markup" if you'd prefer. I've also attached a key I used as a cross reference comments since some responses point to others. This is in my short had so may not be as useful for you. Let us know if you have questions or concerns.
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, April 29, 2020 1:43 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Draft Perchlorate Response to Comment Document

Hi Lisa,

Attached is the draft Perchlorate RtC Document. I incorporated the final input provided by ORD. This version also includes annotated comments from reviewers. Let me know if we should also provide a clean copy for review at this stage.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
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Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
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Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/21/2020 3:15:18 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: FW: Revised Document
Attachments: Perchlorate Reduction Outreach Plan v2.docx; Perchlorate Reductions 2-19-20 v1.docx; Perchlorate Recommendations for PWS 2-21-20.docx

Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

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Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

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Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
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Subject: FW: Revised Document

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Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
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"USEPA Protecting Human Health and the Environment"

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Samuel Hernández Quiñones, P.E.
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"USEPA Protecting Human Health and the Environment"

Message

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Sent: 3/3/2020 9:36:59 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]
CC: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: FW: Materials for tomorrow's Briefing: Perchlorate
Attachments: Decision for Perchlorate Final Regulatory Action_2_26_20.docx; Option Selection for Perchlorate_final_01.09.2020.pdf

Jennifer: Attached are the materials that we would add to the recommendations and reductions documents (that were transmitted to OW) for a discussion with the Administrator. We note that the schedules in the briefing we gave the Administrator on 1/9/20 are now out of date. Below is an update for the withdrawal schedule that assumes a meeting occurs on March 16.

Perchlorate Schedule - Draft 2/24/2020			
Activity	**start**	**end**	**No. Days**

Ex. 5 AC/AWP/DP

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 1/7/2020 8:22:31 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
CC: Wendelowski, Karyn [wendelowski.karyn@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: Revised Perchlorate Briefing
Attachments: Option Selection for Perchlorate 1-9-20v1.docx

Jennifer and Carrie:
Attached for your review and comment is a revised Perchlorate Option Selection briefing that reflects the direction I heard in the discussion today including;

Ex. 5 AC/AWP/DP

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 12/2/2019 9:35:35 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
CC: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
Subject: Perchlorate Briefing Document
Attachments: Redline-Responses - Option Selection for Perchlorate 11-21-19 v1 jlmkw.docx; Clean Version - Option Selection for Perchlorate 12-2-19 v1.docx

Jennifer
Attached are a clean and redline copy of the perchlorate briefing document with your edits incorporated and your comments/questions addressed. If you are comfortable with the attached I recommend you transmit the clean version to OW and that we bring a copy to OLEM for our discussion tomorrow.

Eric

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/28/2020 1:43:16 PM
To: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
CC: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: FW: Revised Document
Attachments: Perchlorate in DW.CB.pdf

Rajiv and Sam: Can you take a look at the attached comments

From: Tiago, Joseph <Tiago.Joseph@epa.gov>
Sent: Thursday, February 27, 2020 12:38 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: Revised Document

Please find attached Charlotte's comments on the perchlorate documents. Thanks!

From: Tiago, Joseph
Sent: Wednesday, February 26, 2020 1:03 PM
To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Revised Document

Sent. Thanks!

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Wednesday, February 26, 2020 11:49 AM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Revised Document

Thank you all! These look great.

Joe – please send the attached versions forward to OW.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 26, 2020 8:21 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: Attached please find clean copies of the recommendations and reductions documents for perchlorate. We have incorporated your edits. Please note with respect to your question about CCR reporting of perchlorate monitoring

CCR regulations under 141.153.(d)(1) requires the CCR include data on detected contaminants subject to mandatory monitoring including

i. Contaminants subject to an MCL, action level, MRDL or TT
ii. Contaminants for which monitoring is required under the UCMR
iii. Disinfection byproducts or micriobial contaminants for which monitoring is required.

Therefore if a system monitors for perchlorate outside of UCMR there is no requirement to report it on the CCR. If a system monitored for perchlorate in the UCMR 1 and detected it, then they were required to report it on the CCR for the next 5 years because 141.153(d)(3)(ii) UCMR results "need only be included in CCR for 5 years from the date of last sample or until any of the contaminants becomes regulated and subject to routine monitoring requirements, whichever comes first."
ASDWA is making arrangements for us to speak with the impacted States on Friday and or Monday morning.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Sunday, February 23, 2020 9:13 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Thank you Eric & Lisa – The attached contain a very few edits/comments. And then, these are ready to go to OW for review. Regarding the outreach plan, continue to pursue the discussions with ASDWA and AWWA as we discussed and agreed to with Dave. However, I'm not sure that we can say these reports will be released soon, maybe it is better to say that there is the potential for them to be issued in the near term.

Thanks much,
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 21, 2020 10:15 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
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Sent: 2/12/2020 2:52:57 PM
To: McLain, Jennifer L. [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]
CC: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
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Sent: 2/24/2020 4:37:56 PM
To: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: FW: Revised Document
Attachments: Perchlorate Recommendations for PWS 2-21-20.docx; Perchlorate Reductions 2-19-20 v1.docx

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From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, February 21, 2020 10:15 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Revised Document

Jennifer: We have updated the recommendations document to reflect the comments you provided earlier. Attached also is a plan to contact States and AWWA next week to verify our information and discuss with the states what assistance might be provided.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Burneson, Eric
Sent: Thursday, February 20, 2020 4:19 PM

To: McLain, Jennifer L. <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Subject: RE: Revised Document

Jennifer;
Attached please find revised perchlorate documents. We have revised the perchlorate reductions document with a view towards public release. We have also prepared the attached plan to work next week with ASDWA and AWWA to verify information about the systems and prepare states to assist systems.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: McLain, Jennifer L.
Sent: Wednesday, February 12, 2020 11:24 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: RE: Revised Document

Eric – would you please review this document with an eye towards the future public version. Once you have a chance to talk to the team, I would appreciate a plan for stakeholder engagement/outreach.

Thanks
Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM

To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 11/15/2019 7:32:13 PM
To: Albert, Ryan [Albert.Ryan@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: FW: Revised briefing document - Perchlorate
Attachments: Option Selection for Perchlorate 11-15-19 v1.docx

Let me know if you would like to discuss further. I have asked Sam to get together with Rich to compare the % of systems above the HRL for the negative and deferred reg det 4 contaminants to the % of systems above the potential MCLG/MCL of 18 ppb for perchlorate. I want us to convey how proceeding with the perchlorate regulation is potentially precedent setting and or conflicting with future reg det decisions.

From: Burneson, Eric
Sent: Friday, November 15, 2019 2:15 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Albert, Ryan <Albert.Ryan@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Weisman, Richard <Weisman.Richard@epa.gov>
Subject: RE: Revised briefing document - Perchlorate

Sam:
Thank you for preparing a revised briefing to respond to the input received in our prebrief. I have made additional edits to address requests received from OW leadership. I have left sections highlighted where OGC input is still needed. I also need you to work with the Regulatory Determinations team to assure we have accurate comparisons of frequency of occurrence in systems at levels above the HRL for Reg Det 4 contaminants and perchlorate occurrence above the MCLG/MCL.
We will not be briefing the Administrator for the next several weeks but we do have an opportunity for OW review of the document so lets try to have revisions next week.
Please include OST on the next version. I have copied Betsy on the attached so that she can see the latest but you should also share with Greg and Jamie.

Eric

From: Hernandez-Quinones, Samuel
Sent: Wednesday, November 13, 2019 12:32 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Revised briefing document - Perchlorate

Hi Eric,

Attached is a revised version of the briefing document, based on Jennifer's direction and comments during last week's meeting. Lisa reviewed this version and provided additional edits. I left two placeholders in this document for the input from OLEM as well as from OGC.

I sent this draft version to Karyn and she is working on providing OGC's input to us. Let me know if you have comments or any suggested edits.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 12/2/2019 3:38:00 PM
To: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
CC: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: FW: Perchlorate
Attachments: Option Selection for Perchlorate 11-21-19 v1 jlmkw.docx

Lisa:
Can you review the attached briefing with Jennifer and Karyn's edits to confirm we are comfortable edits and have addressed the questions.
Please note that Betsy Behl stated she is comfortable and I have contacted OLEM about scheduling the meeting.

Eric

From: Wendelowski, Karyn
Sent: Wednesday, November 27, 2019 10:51 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Subject: Re: Perchlorate

Hi Eric - attached are a few edits and responses to Jennifer's questions. I've also let DOJ know the decision is now likely to occur mid-December.

Karyn

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, November 26, 2019 4:24 PM
To: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Subject: RE: Perchlorate

Karyn:
The briefing has not happened nor is it scheduled. I have asked the team to assume that we will not brief the Administrator until mid December based upon input from OW – IO. Attached is a revised briefing from Jennifer McLain.

If you are in tomorrow it would be good to get your input on a few questions related to this briefing. Thanks

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Wendelowski, Karyn
Sent: Tuesday, November 26, 2019 1:33 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Albert, Ryan <Albert.Ryan@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Weisman, Richard <Weisman.Richard@epa.gov>
Subject: Perchlorate

Hi All: - DOJ has asked me to check in with you on where we are with respect to schedule and timing. Has a briefing occurred? Any decisions?

Thanks (and Happy Thanksgiving),

Karyn

Karyn Wendelowski
Attorney-Advisor
Water Law Office
Office of General Counsel
(202)564-5493

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 11/21/2019 8:16:25 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: RE: Perchlorate briefing
Attachments: Option Selection for Perchlorate 11-21-19 .docx

Thank you Sam: A few comments in the attached and an assumption to use Dec 13 as the date of the Administrators briefing. Can you adjust the schedule and get this back to me?
Thanks
Eric

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Tuesday, November 19, 2019 9:43 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric,

I have incorporated your edits as well as the additional occurrence data provided by the Reg Det Team, and the new input from OGC.

Please take particular attention to the edits I made to the language you inserted in the "Rationale" section of Option 1. I made the edits considering the data provided by the Reg Det Team.

Let me know if you have any comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, November 15, 2019 2:16 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Sam I just sent you my comments on the previous version. Let me know if there are edits you made in your version that need to be incorporated into mine.

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Friday, November 15, 2019 2:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate briefing

Hi Eric,

I have updated the briefing document after talking with Lisa Huff about the additional edits you wanted to see in the document.

I have also incorporated OGCs input into this version of the briefing document, which contains language about their legal strategy and the implications on the schedule. Let me know if you have any comments or if you would like us to include any additional information.

Thanks

Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

-----Original Message-----
From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Thursday, November 14, 2019 4:32 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Re: Perchlorate briefing

Thanks Sam. Looks like you have the relevant points other than Eric said we should put as an option the MCLG if 18 not the other values. I'll talk to you in the morning and we can see what Eric wants to see.

Lisa

> On Nov 14, 2019, at 3:51 PM, Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov> wrote:
>
> Hi Lisa,
>
> I sent a revised draft version of the briefing document to Eric earlier this week. We are waiting for additional input that OGC will provide to us. Here is the revised document, as reviewed by Lisa, that I shared with Eric. If you have additional information, I will be glad to incorporate into the document.
>
> I will be in the office tomorrow morning if you want to hand those notes to me, or you can also email them.
>
> Thanks
> Sam
> ==========
> Samuel Hernández Quiñones, P.E.
> Environmental Engineer
> Office of Water
> Environmental Protection Agency
> 1200 Pennsylvania Ave. NW
> Washington, DC 20460
> 202-564-1735
>
> "USEPA Protecting Human Health and the Environment"
>
> -----Original Message-----
> From: Huff, Lisa <Huff.Lisa@epa.gov>
> Sent: Thursday, November 14, 2019 3:37 PM
> To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
> Cc: Christ, Lisa <Christ.Lisa@epa.gov>
> Subject: Perchlorate briefing
>
> Sam,
> I just had a conversation with Eric. He said the meeting with with Dave Ross and the Administrator has been delayed however he said we need to put together the briefing materials ASAP. He gave me a brief summary of the 3 options to reflect based on direction from last week. I can email you those point but thought you might have in your notes. He had one addition that is for the option recommending a MCL we should specify that value would be 18. Have you been working on preparing materials? Eric was hoping to have them by tomorrow for his review. Please let me know. I'm out of the office for an appt. but will follow up via email shortly.
>
> Lisa
> <Option Selection for Perchlorate 11-12-19 v1.docx>

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/18/2020 4:18:38 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
Subject: RE: 2 perchlorate documents -- for your records
Attachments: Perchlorate Reductions 2-18-20_rk-egb.docx

Thank you Sam and Rajiv for your work to address my comments. I have a few more follow up request in the attached. Can you see if we can get OLEM to expedite their feedback on the table? Putting forward this document is critical to getting decisions needed to make the court filing.
Eric

From: Hernandez-Quinones, Samuel
Sent: Tuesday, February 18, 2020 10:23 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Hi Eric, please see attached document. It incorporates your suggested edits and addresses your questions.

I am also waiting for some additional feedback form OSWER on the table they provided, as they way it reads now it appears to show several entries for the same mitigation site. Depending on their feedback we might have to update that table.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Huff, Lisa <Huff.Lisa@epa.gov>
Sent: Tuesday, February 18, 2020 10:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Yes I'll check with Sam and get back to you.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, February 18, 2020 10:07 AM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: 2 perchlorate documents -- for your records

Lisa:
I sent the attached comments to Lisa Christ on Thursday but I don't think I received a revised document. Since Lisa is out today, can you check with the Team to get me a revised today?
Thanks
Eric

From: Burneson, Eric
Sent: Thursday, February 13, 2020 2:05 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: 2 perchlorate documents -- for your records

Thank You Lisa
I have a few comments/edits on the perchlorate reduction document in the attached.
Eric

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:59 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: 2 perchlorate documents -- for your records

Eric – just wanted to put both documents in one place for you. Both have been reviewed by Jennifer and Christina. Lisa

---

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, February 12, 2020 9:53 AM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Revised Document

Attached is the update on systems and perchlorate reductions. The only outstanding system is in LA.

From: Christ, Lisa
Sent: Wednesday, February 12, 2020 9:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Revised Document

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 12:37 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Hi Lisa,

We got new information from the MD system. There was some misunderstanding with the information request but here is the latest.

The treatment plant at chapel hill was recently taken off line and it was replaced with new productions wells and treatment plant which started operations in January 27, 2020. Please see the new language that I have incorporated in the revised document below.

"EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that the Chapel Hill WFP was taken off line and it was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicated that monitoring was conducted in November 2019 and the analysis shows that perchlorate was not detected in either the source well water or the finished water."

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Monday, February 10, 2020 10:31 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Document

Thanks Sam.
Do we know exactly what the contractor asked each PWS? Based on this response: **EPA contacted the Chapel Hill System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate is available.** It appears we only asked about monitoring…did the contractor ask about any changes in source water and/or treatment too?

Thanks,
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, February 10, 2020 8:14 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Revised Document

Hi Lisa,

We heard back from the Chapel Hill system in MD and they do not have new data for Perchlorate. The document has been updated accordingly. Please see attached.

Thanks
Sam
==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 1/3/2020 6:03:12 PM
To: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]
CC: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
Subject: Perchlorate briefing
Attachments: Option Selection for Perchlorate 12-20-19v4.docx

Lisa:
I received comments from Jennifer on the perchlorate briefing and the attached reflects those comments. The most significant ask is to present the total population vs protected population breakdown as shown on page 4. Let me know if you have any concerns or if it is not possible to make the requested changes before noon on Monday. Thanks

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 1/22/2020 4:01:46 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
Subject: RE: FOR REVIEW: Perchlorate Reductions Over Time
Attachments: Reductions of Perchlorate in Drinking Water 1-22-20 .docx

Lisa:
Thank you and the team for the great work in preparing this document. I have some comments and edits in the attached. Please let me know if you have any concerns or questions.
Eric

From: Christ, Lisa
Sent: Tuesday, January 21, 2020 1:48 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: FOR REVIEW: Perchlorate Reductions Over Time

Eric,
Attached is the document describing reductions in perchlorate since UCMR1. We worked with OPP on the labeling language and with OLEM on the list of superfund sites. Water systems that are being contacted by Abt are highlighted yellow. We're in the process of modifying the PWS recommendations and will have that ready for Jennifer soon.
Let us know if you have questions or concerns.
Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, January 17, 2020 5:14 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: RE: FOR REVIEW: Perchlorate Recommendations for PWS

Lisa and team:
Thank you for the great work to prepare this document so quickly. It is a great. I do have a number of edits and comments but I believe we are heading in the right direction. Please look at my comments in the attached and let me know if you would like to discuss on Tuesday or Wednesday.
The next draft should get input from our Comms director which is why I have copied Christina so that she can start thinking about how she would like to present this information.

Thanks again for the great work.
Eric

From: Christ, Lisa
Sent: Thursday, January 16, 2020 10:05 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>;

Alattar, Zaineb <alattar.zaineb@epa.gov>
Subject: FOR REVIEW: Perchlorate Recommendations for PWS

Hi Eric,
Attached is the draft document of recommendations for PWS that may be concerned about perchlorate in drinking water. We are still working on the other document. Let us know if you have questions, etc.

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 9/12/2019 4:10:34 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]
Subject: Perchlorate comment summary
Attachments: Perchlorate Comment Summary V4.docx

Jennifer and Yu Ting:
Attached please find a summary of the comments on the proposed perchlorate drinking water regulation. This issue came up in the hearing prep meeting for the Administrator yesterday and I would like to present the attached in the OW biweekly tomorrow. Please let me know if you have any comments or concerns with the attached.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

NPDWR for Perchlorate Proposal: Summary of Public Comments

EPA received a total of 1,495 comments in response to its perchlorate rulemaking proposal.

Mass Mailing Campaign: 1,386 comments were received under a mass mailing campaign. These commenters oppose the proposed Maximum Contaminant Level of 56 µg/L stating that as proposed the MCL is too high to adequately protect the health of communities throughout the country.

Individuals: Eighty-one comment letters with varied levels of complexity were submitted by individuals. These letters cover a wide array of technical and policy issues regarding the perchlorate proposal (88 pages).

6 support the 56 µg/L proposal.
1 supports the 90 µg/L alternative.
6 support the 18 µg/L alternative.
23 support regulation at a level lower than 18 µg/L.
1 supports the withdrawal of the regulatory determination.
44 are in general opposition and/or out of scope.

Extensive and Substantive Comment Letters from Organizations: Twenty-eight comment letters containing extensive and substantive technical and policy issues were submitted (657 pages). The overall recommendation of these comment letters on the regulatory proposal breakdown as follows.

- One organization did not take a position regarding regulation of perchlorate:
  - Association of State Drinking Water Administrators
- None support the proposed 56 µg/L proposal.
- None support the 90 µg/L alternative.
- Two support the 18 µg/L alternative:
  - Oregon
  - Virginia
- Fourteen support regulation at a level lower than 18 µg/L:
  - Association of California Water Agencies
  - Metropolitan Water District of Southern California
  - California
  - Massachusetts
  - New Jersey
  - New York
  - The Salt River Pima-Maricopa Indian Nation
  - The Tohono O'odham Nation
  - Alaska Community Action on Toxics
  - Environmental Defense Fund
  - Environmental Protection Network
  - Environmental Working Group
  - Natural Resources Defense Council
  - American Academy of Pediatrics

NPDWR for Perchlorate Proposal: Summary of Public Comments

- Eleven support withdrawal of the determination to regulate perchlorate:
  - U.S. Conference of Mayors & the National League of Cities (joint letter)
  - South Dakota
  - California Farm Bureau Federation
  - American Water
  - El Paso Water
  - American Chemistry Council
  - American Water Works Association
  - Association of Metropolitan Water Agencies
  - National Rural Water Association
  - Perchlorate Study Group
  - The Chlorine Institute

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/15/2019 2:05:45 PM
To: Nickerson, William [Nickerson.William@epa.gov]
Subject: FW: Revised Perchlorate FRN and related items (to go TO OP today
Attachments: FINAL REDLINE - EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412 (002).docx

Attached is a track changes that shows what changed between the version we sent previously to OP and the version that was sent on Friday (including deleting reference to schizophrenia in the list of health effects on page 14.).

From: Corr, Elizabeth
Sent: Friday, April 12, 2019 3:30 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: FW: Revised Perchlorate FRN and related items (to go TO OP today

Appended below is confirmation from Macara's staff that the package went to OP today. (Sent electronically rather than hard copy, per Macara, since this is a revised draft under review.)

The attached Track version (same as provided in clean copy to OW and OP) documents the final round of edits made in SRMD and OGWDW. Lisa C has the email sent to OW with all attachments.

From: Evalenko, Sandy
Sent: Friday, April 12, 2019 2:45 PM
To: Corr, Elizabeth <Corr.Elizabeth@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Wadlington, Christina <Wadlington.Christina@epa.gov>
Subject: Re: Revised Perchlorate FRN and related items (to go TO OP today

FYI I sent this forward to Leanne Nurse.

Sent from my iPhone

On Apr 12, 2019, at 1:45 PM, Corr, Elizabeth <Corr.Elizabeth@epa.gov> wrote:

> HRRCA, transmittal, action memo, pdf of Jennifer's signature, and FRN. Pls let us know if anything else is needed to get the package to OP today. (I will be here til 3 PM.)
> Many thanks.
>
> ---
>
> **From:** Christ, Lisa
> **Sent:** Friday, April 12, 2019 11:38 AM
> **To:** Corr, Elizabeth <Corr.Elizabeth@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
> **Cc:** Tiago, Joseph <Tiago.Joseph@epa.gov>
> **Subject:** FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos
>
> FYI ---

From: Christ, Lisa
Sent: Friday, April 12, 2019 10:52 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <khera.rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: FW: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi Jennifer,
Attached for your transmittal to OW are the following:
The FRN for the NPDWR for Perchlorate, proposed rule (a clean and a track changes version for convenience)
Health Risk Reduction Cost Analysis
Transmittal/Action memos

Let us know if you need anything else.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, April 12, 2019 10:44 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: Revised Perchlorate FRN, HRRCA & Transmittal Memos

Hi,

Attached are the revised clean versions of the Perchlorate FRN and HRRCA, which incorporate all the suggested edits to date (4-12-19).

Here also you will find a revised redline version which incorporates all edits and changes to the document made to the FRN since the last OW-IO review (3-11-19).

Finally, attached are the most recent version of the corresponding transmittal memos.

Let me know if you have any questions or comments.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

<EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate HRRCA 20190412.docx>

<Transmittal Memo JM to DR 4-9-19.docx>

<Perchlorate Draft Action Memo 4-9-19.docx>

<image2019-04-12-134922.pdf>

<EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190412.docx>

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/15/2019 1:58:16 PM
To: Nickerson, William [Nickerson.William@epa.gov]
Subject: FW: Perchlorate
Attachments: Perchlorate Proposed NPDWR Redline 4-5-19.2.docx

Bill
This contains Lindsey's comments which we addressed in the document that was transmitted on Friday. Regarding her schizophrenia comment, we deleted mention of it where she noted her concern (page 14). We have retained the discussion of the Gyllenberg paper later in the document (around page 100 in the document sent Friday) to be comprehensive in our discussion of all the studies examining the link between thyroid hormone perturbation and behavioral outcomes. This is to be consistent with presenting the information that was peer reviewed and to be responsive to comments that did/did not find statistically significant relationships.
Eric

From: Forsgren, Lee
Sent: Thursday, April 11, 2019 5:19 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Perchlorate

Jennifer and Eric,

If Jennifer's comments can be easily incorporated do it. It looks like she might strengthen our case. If not ignore them and we can work with her later.

Lee

From: Jones, Lindsey
Sent: Thursday, April 11, 2019 4:54 PM
To: Forsgren, Lee <Forsgren.Lee@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>
Cc: Ross, David P <ross.davidp@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>
Subject: RE: Perchlorate

Hi Lee,

I provided some additional comments on Nancy's draft. Could you also tell me where this is in the review process? Is this the latest version or will we be getting another?

Thank you,
Lindsey

From: Forsgren, Lee
Sent: Wednesday, April 10, 2019 1:19 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>
Cc: Jones, Lindsey <jones.lindsey@epa.gov>; Ross, David P <ross.davidp@epa.gov>
Subject: RE: Perchlorate

Nancy,

Appreciate that there isn't much time to review but we are facing a very tight court ordered timeline to publish a proposed MCLG. That deadline is May 28th and the Administrator is facing a contempt of court citation if we fail to meet that deadline. As you might guess his direction has been clear that we will not put him is a circumstance where he is in contempt of court.

We will certainly add text to clarify the uncertainties and shortcomings of some of the literature in the areas that you identified and incorporate a reference to the agency's data derived extrapolation factors. We did discuss it in the context of cost benefit but can certainly address them in the context of the MCLG.

As for the IQ section – the discussion is there per the direction/agreement with OMB and is the basis of the agreed upon approach to discussion of how to address IQ. It was based on this agreement that they would now accept the draft for interagency review. That general discussion of IQ, and the underlying uncertainty of value to individuals but importance on a population basis, is the intellectual basis for why we are proposing a preferred option of two IQ points but why we are taking comments on values above and below, as well as to withdraw the determination to regulate.

If you believe it is inconsistent with the Administrator's approach on IQ in the context of lead we need to have that discussion with the Administrator, Dave Ross, Alex Dunn and others, ASAP after the draft has gone into interagency review because of the tight timeline we are under regarding the court order.

If you have any other questions please let me know.

Regards,
Lee

D. Lee Forsgren
Deputy Assistant Administrator
Office of Water
Environmental Protection Agency
1200 Pennsylvania, Avenue NW
Room 3219B WJC East Building
Washington, DC 20460
202-564-5700

From: Beck, Nancy
Sent: Wednesday, April 10, 2019 11:37 AM
To: Mejias, Melissa <mejias.melissa@epa.gov>
Cc: Forsgren, Lee <Forsgren.Lee@epa.gov>; Jones, Lindsey <jones.lindsey@epa.gov>
Subject: RE: Perchlorate

Melissa and Lee,
Thanks for the opportunity to review. I am hugely swamped trying to get 2 of our rules and 2 risk evaluations over to OMB so I could only review very quickly.
I looked back at some of our previous comments and flagged a few that I don't think were addressed. I also notice that your team did address many of our previous comments—thank you for that!
I also flagged the new IQ section—It gives me some heartburn based on where the Administrator wanted us to go in our lead rules, so I flagged that for you.

Lindsay may have additional thoughts/more time to review.

Thanks again,
Nancy

Nancy B. Beck, Ph.D., DABT
Principal Deputy Assistant Administrator, OCSPP
P: 202-564-1273
beck.nancy@epa.gov

From: Mejias, Melissa
Sent: Tuesday, April 9, 2019 10:39 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Forsgren, Lee <Forsgren.Lee@epa.gov>
Subject: Perchlorate

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 9/11/2019 3:59:52 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: draft summary of perchlorate public comments
Attachments: Perchlorate Comment Summary V3.docx

Thanks Lisa this breakdown is helpful but it pointed out to me that the 109 extensive and substantive letters don't all appear to be summarized.
I think there isn't a need to organize the commenters by organization type and there are some groups that are hard to categorize (i.e. we have ACWA as a regulated stakeholder but AWWA is a trade organization when the both represent drinking water utilities) I also think there is redundancy in the summary of the comments that I tried to eliminate in the attached.
Can the team take a look and see if there are organizations that have submitted extensive and substantive comments that we have not listed and if so please list them in the categories of support that are in the attached.

From: Christ, Lisa
Sent: Wednesday, September 11, 2019 7:46 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: draft summary of perchlorate public comments

Revised

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, September 10, 2019 4:04 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Hi Lisa,

Here is a revised version which incorporates previously suggested edits.

- We received 6 comment letters in support of the proposed rule at 56 ppb.
- I cannot categorically confirm that the mass mailing campaign was organized by any group, so I am removing that designation from the summary document.
- From the individual substantive letters
  - 1 supports withdrawal option
  - 1 supports 90 ppb option
  - 6 support 18 ppb option
  - 23 support regulation at a stricter level than 18pbb

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, September 10, 2019 1:44 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: draft summary of perchlorate public comments

Hi Sam,
As follow up can you please:

- Confirm we did not get support for regulation at 56 ppb
- Confirm if NRDC is mentioned as the originator of the mass campaign
- Count the 88 individual comments that 1- support withdrawal, 2- support regulation (at any concentration).

Let me know if you have questions
Thanks,
Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, September 10, 2019 1:30 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Also There are three categories of commenters presented

1. Support withdrawal
2. Support a stricter than proposed standard
3. Neutral

Does this mean there were no commenters in support of the proposed MCLG/MCL?

From: Burneson, Eric
Sent: Tuesday, September 10, 2019 1:27 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: draft summary of perchlorate public comments

Thanks Lisa: My only comment is that unless the comment campaign letters clearly state they are submitting comments organized by NRDC or there is public information from NRDC clearly stating that they organized a comment campaign we should not attribute the campaign to them.
Eric

From: Christ, Lisa
Sent: Tuesday, September 10, 2019 12:27 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Lombardi, Thomas <lombardi.thomas@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: draft summary of perchlorate public comments

Eric,
Attached is a high level summary of the public comments received on the perchlorate proposal. OGC requested a summary to prepare the notice to the court requesting an extension of the consent decree final rule deadline. Let me know if you have questions or would like to discuss.
Lisa

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

NPDWR for Perchlorate Proposal: Summary of Public Comments

NPDWR for Perchlorate Proposal: Summary of Public Comments

EPA received a total of 1,495 comments in response to its perchlorate rulemaking proposal.

Mass Mailing Campaign:

11,386 comments were received under a mass mailing campaign. These commenters oppose the proposed Maximum Contaminant Level of 56 µg/L stating that as proposed the MCL is too high to adequately protect the health of communities throughout the country.

Individuals:

Eighty-one comment letters with varied levels of complexity were submitted by individuals. These letters cover a wide array of technical and policy issues regarding the perchlorate proposal (88 pages).

6 individuals support the 56 µg/L proposaled rule a 56 µg/L.

1 individual supports the regulatory determination withdrawal alternative

1 individual supports the 90 µg/L alternative.

23 6 individuals support the 18 µg/L alternative.

23 individuals support perchlorate regulation at a level lower stricter than 18 µg/L ppb

1 individual supports the withdrawal of the regulatory determination withdrawal alternative

Extensive and Substantive Comment Letters from Organizations:

109 Comment letters containing extensive and substantive technical and policy issues were submitted (657 pages).

The overall recommendation of these comment letters on the regulatory proposal breakdown as follows:

- One organization did not take a position regarding regulation of perchlorate.
  - Association of State Drinking Water Administrators
- None support the proposed 56 µg/L proposal.
- None support the 90 µg/L alternative.
- # support the 18 µg/L alternative.
  - Oregon
  - Virginia
- # support regulation at a level lower than 18 µg/L
  - Association of California Water Agencies

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Commented [BE1]: There are not 109 letters described below. I count 28. Is this a breakdown or some key highlights of selected letters? If its key highlights then we need a breakdown of the 109 similar to the breakdown for the individuals above

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- Metropolitan Water District of Southern California
- California
- Massachusetts
- New Jersey
- New York
- The Salt River Pima-Maricopa Indian Nation
- The Tohono O'odham Nation
- Alaska Community Action on Toxics
- Environmental Defense Fund
- Environmental Protection Network
- Environmental Working Group
- Natural Resources Defense Council
- American Academy of Pediatrics

~~# 1. Organizations that~~ support withdrawal ~~of the determination to regulate perchlorate~~:

*

U.S. Conference of Mayors & the National League of Cities ~~(joint letter)~~

~~One letter was jointly submitted by the U.S. Conference of Mayors & the National League of Cities. These organizations urge EPA to withdraw the Regulatory Determination for Perchlorate.~~

~~State Agency~~

~~*South Dakota~~

South Dakota ~~Department of Environment and Natural Resources—Recommends that EPA withdraw the Regulatory Determination based on a no meaningful opportunity for risk reduction as required by SDWA~~

~~Regulated Stakeholders/Community Water Systems~~

~~Two comment letters were submitted by Regulated Stakeholders/Community Water Systems.~~

*American Water

*El Paso Water

~~American Water & El Paso Water—Recommend EPA withdraw the Regulatory Determination~~

~~Trade/Industry Associations~~

~~Seven comment letters were submitted by Trade/Industry Associations~~

*American Chemistry Council

*American Water Works Association

*Association of Metropolitan Water Agencies

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- National Rural Water Association
- Perchlorate Study Group
- The Chlorine Institute
- ~~California Farm Bureau Federation~~

~~American Chemistry Council, American Water Works Association, Association of Metropolitan Water Agencies, California Farm Bureau Federation, The Chlorine Institute, Perchlorate Study Group, National Rural Water Association – Recommend that EPA withdraw the Regulatory Determination based on not meeting the statutory requirements of SDWA.~~

~~2. Organizations that support stricter (than proposed 56 ppb) regulation of perchlorate:~~

~~Regulated Stakeholders/Community Water Systems~~

~~Two comment letters were submitted by Regulated Stakeholders/Community Water Systems~~

- ~~Association of California Water Agencies~~
- ~~Metropolitan Water District of Southern California~~
- ~~Association of California Water Agencies & Metropolitan Water District of Southern California – Urge EPA to set an MCLG and MCL close to California's standard of 6 µg/L. The federal drinking water standard should be no higher than 18 µg/L.~~

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~~State Agencies~~

~~Six comment letters were submitted by State Agencies~~

- ~~California~~
- ~~Massachusetts~~
- ~~New Jersey~~
- ~~New York~~
- ~~Oregon~~
- ~~Virginia~~
  - ~~California – Does not agree with EPA's proposal because it is not health-protective and also believe that the agency has taken approaches that are not fully justified, not appropriate, and that need to be reconsidered.~~
  - ~~Massachusetts – Does not support EPA's proposed options for perchlorate in drinking water. MassDEP urges EPA to revise its proposal to fully address perchlorate's toxicity and health protective uncertainty factors.~~
  - ~~New Jersey – Does not agree with EPA's proposal and recommends additional assessments on the approach to develop Reference Doses as well as the adequacy of the utilized Uncertainty Factors and the IQ benchmarks.~~

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- ~~New York – Does not agree with EPA's proposal and recommends additional technical assessments to better define the basis and policy choices for adverse neurodevelopmental effects on children.~~

- ~~Oregon – Recommends EPA to adopt an MCL of 18 µg/L rather than 56 µg/L.~~

- ~~Virginia – Recommends EPA to adopt an MCL of 18 µg/L based on possible occurrence above such level due to hypochlorite degradation in the distribution system.~~

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~~Tribal Stakeholders~~

~~Two comment letters were submitted by Tribes~~

- ~~The Salt River Pima-Maricopa Indian Community & the Tohono O'odham Nation – Submitted letters in disagreement with EPA's proposal, and urged the agency to establish an MCL at a level lower than 18 µg/L.~~

Formatted: List Paragraph, Bulleted + Level: 1 + Aligned at: 0.75" + Indent at: 1"

~~Environmental Advocacy Groups~~

~~Five comment letters were submitted by Environmental Advocacy Groups (305 pages)~~

- ~~Alaska Community Action on Toxics~~
- ~~Environmental Defense Fund~~
- ~~Environmental Protection Network~~
- ~~Environmental Working Group~~
- ~~Natural Resources Defense Council~~

~~These groups strongly disagree with EPA's rulemaking proposal and the suggested regulatory alternatives. All groups suggest that EPA should set a standard for Perchlorate in drinking water no higher than 2 µg/L. In addition, these stakeholders claim that EPA is not following the statutory requirements of SDWA in that the agency failed to consider an adequate margin of safety while establishing a protective public health MCLG.~~

~~Public Health Professional Organizations~~

~~American Academy of Pediatrics – Disagree with EPA's proposal and urges the agency to set the strongest possible MCLG for Perchlorate.~~

~~3. Organizations that are neutral~~

~~Association of State Drinking Water Administrators – The board has not taken a position on whether to regulate Perchlorate.~~

Formatted: List Paragraph, Indent: Left: 0"

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/23/2019 2:05:54 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]
Subject: RE: perchlorate
Attachments: EPA Responses to EO12886 Comments - HRRCA Perchlorate NPDWR 5-23-19 .docx; EPA Response to OMB edits Perchlorate NPDWR FRN 05-23-19.docx

Attached please find my draft responses.
Sam please verify the acceptance of edits on the FRN and insert the footnote on the benefits uncertainty table.
Rajiv please verify my edit to the benefits dietary consumption and let Sam and I know if there are further edits required

From: Burneson, Eric
Sent: Thursday, May 23, 2019 9:44 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: FW: perchlorate

Please review ASAP and let me know if there are any show stoppers

From: Dorjets, Vlad EOP/OMB [mailto:Vladik_Dorjets@omb.eop.gov]
Sent: Thursday, May 23, 2019 9:43 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: perchlorate

Final edits.

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 12/12/2018 4:42:27 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: RE: Revised Version - Perchlorate FRN
Attachments: Version-Control Perchlorate Rule FRN 12-7-18egb.docx

Lisa:
I am very grateful for the excellent work the Team has done to prepare this revised proposal. I have just a few edits in the attached. I will bring you hard copies of the changed pages to expedite incorporating these edits. As we discussed, at this stage we just need a version that incorporates suggested edits. Please remove the comments provided and we can address them with Jennifer at a later date. This way Jennifer can transmit the revised version to OW and we can send a revised version to OGC.

Thanks

From: Mclain, Jennifer
Sent: Tuesday, December 11, 2018 5:52 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Revised Version - Perchlorate FRN

Lisa,
I am so impressed by the quality of the proposal your team put together. The attached includes my edits and comments/questions. If it would be helpful for you all to sit down and go over some of the later, rather than trying to respond in comment bubbles, I'm happy to do that. I am not as well versed on this information as you all so I may have made edits or comments that are not appropriate. If that is the case, please ignore the edit and don't feel the need to explain why.
Thanks much,
Jennifer

From: Christ, Lisa
Sent: Friday, December 07, 2018 3:16 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: Revised Version - Perchlorate FRN

Hi Jennifer,
The attached perchlorate proposal addresses my comments and Eric's. We have some additional information we are working on to provide more context for the HRRCA section. This version is ready for your and OW/OGC review. We'll fold in our additional information in the next round of edits.

Let us know if you have questions or concerns.

Lisa

From: Hernandez-Quinones, Samuel
Sent: Friday, December 07, 2018 3:10 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Revised Version - Perchlorate FRN

Hi Lisa,

Attached is the revised FRN for Perchlorate.

Thanks

Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 1/9/2020 5:52:27 PM
To: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]
Subject: FW: Materials for tomorrow's Briefing: Perchlorate
Attachments: Option Selection for Perchlorate_final_01.09.2020.pdf

---

From: Aguirre, Janita
Sent: Wednesday, January 08, 2020 3:05 PM
To: Bolen, Brittany <bolen.brittany@epa.gov>; Jones, Lindsey <jones.lindsey@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Nagle, Deborah <Nagle.Deborah@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Ross, David P <ross.davidp@epa.gov>
Cc: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; Mejias, Melissa <mejias.melissa@epa.gov>; Penman, Crystal <Penman.Crystal@epa.gov>; Lovell, Will (William) <lovell.william@epa.gov>; Hilosky, Nick <Hilosky.Nick@epa.gov>; Brooks, Becky <Brooks.Becky@epa.gov>; Mutz, John (Fletcher) <mutz.john@epa.gov>; Christian, Megan <Christian.Megan@epa.gov>; Fitzmorris, Amanda <fitzmorris.amanda@epa.gov>
Subject: Materials for tomorrow's Briefing: Perchlorate

All,

The final document for tomorrow's Briefing: Perchlorate with the Administrator is attached.

Thank you,
Janita

Janita Aguirre – Special Assistant
U.S. Environmental Protection Agency | Office of Water
Phone: **(202) 566-1149** | Email: aguirre.janita@epa.gov

Subject: Briefing: Perchlorate
Location: Administrator's Office

Start: Thu 1/9/2020 2:15 PM
End: Thu 1/9/2020 3:00 PM

Organizer: Adm15Wheeler.Calendar
Required Attendees: David Ross (ross.davidp@epa.gov); Mclain, Jennifer; Dunlap, David; Orme-Zavaleta, Jennifer; Wright, Peter; Breen, Barry; Leopold, Matt (OGC); Fotouhi, David; Wehling, Carrie; Nagle, Deborah; Bolen, Brittany; Jones, Lindsey

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/23/2019 1:44:06 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: FW: perchlorate
Attachments: EPA Responses to EO12886 Comments - HRRCA Perchlorate NPDWR 5-22-19 (05-23).docx; EPA Response to OMB edits Perchlorate NPDWR FRN 05-22-19 (OMB 05-22-19) (05-23).docx

Please review ASAP and let me know if there are any show stoppers

From: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP)
Sent: Thursday, May 23, 2019 9:43 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: perchlorate

Final edits.

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Sent: 4/11/2019 11:12:37 PM
To: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]
Subject: FW: perchlorate proposal
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190411 Redlinev4.docx

---

From: Burneson, Eric
Sent: Thursday, April 11, 2019 7:10 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: perchlorate proposal

Attached please find an updated version of the redline document to address some of the additional comments we received from the OW-IO.

From: Burneson, Eric
Sent: Thursday, April 11, 2019 5:39 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: perchlorate proposal

Hold on this I am doing further editing to reflect the additional input we receive in the last hour.

From: Burneson, Eric
Sent: Thursday, April 11, 2019 4:53 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: RE: perchlorate proposal

Jennifer:
I have reviewed and made additional edits to the redline that Sam prepared to reflect the input we received from the OW IO yesterday and today. I believe the attached revisions address the OW IO requests. Can you please review to assure and let Lisa and Sam know if we can send forward the revised documents for transmission to OP? OP has asked that we transmit them by tomorrow.
Thanks in advance.

Eric

From: Christ, Lisa
Sent: Thursday, April 11, 2019 12:48 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: perchlorate proposal

From: Hernandez-Quinones, Samuel
Sent: Thursday, April 11, 2019 12:42 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: perchlorate proposal

Hi Lisa,

Revised document is attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa
Sent: Thursday, April 11, 2019 12:15 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: perchlorate proposal

Sam & Rajiv --

Good news! If you've made the revisions requested yesterday, we have been cleared to send this to OP. Eric would like to see the revisions first. Please send the track change and clean versions to Eric and me as soon as possible. We'll do a quick review and transmit to OP.

THANKS! This has been a huge effort and I really appreciate all the hard work

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/11/2019 11:12:09 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: RE: perchlorate proposal
Attachments: Perchlorate Proposed NPDWR Redline 4-5-19.2.with replys.docx

I inserted replies to each of the comments in the attached version. Note that I did not make the corresponding edits in this document but those edits are in the revised version I sent you a few minutes ago.

From: Mclain, Jennifer
Sent: Thursday, April 11, 2019 6:18 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Re: perchlorate proposal

I'm not sure it is possible to address all of those comments.

Jennifer

On Apr 11, 2019, at 5:39 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

> Hold on this I am doing further editing to reflect the additional input we receive in the last hour.
>
> ---
>
> **From:** Burneson, Eric
> **Sent:** Thursday, April 11, 2019 4:53 PM
> **To:** Mclain, Jennifer <Mclain.Jennifer@epa.gov>
> **Cc:** Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
> **Subject:** RE: perchlorate proposal
>
> Jennifer:
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> Thanks in advance.
>
> Eric
>
> ---
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> **From:** Christ, Lisa
> **Sent:** Thursday, April 11, 2019 12:48 PM
> **To:** Burneson, Eric <Burneson.Eric@epa.gov>
> **Subject:** FW: perchlorate proposal
>
> ---
>
> **From:** Hernandez-Quinones, Samuel
> **Sent:** Thursday, April 11, 2019 12:42 PM
> **To:** Christ, Lisa <Christ.Lisa@epa.gov>

Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: perchlorate proposal

Hi Lisa,

Revised document is attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Christ, Lisa
Sent: Thursday, April 11, 2019 12:15 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: perchlorate proposal

Sam & Rajiv --

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THANKS! This has been a huge effort and I really appreciate all the hard work

Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/11/2019 11:09:59 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
CC: Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: RE: perchlorate proposal
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190411 Redlinev4.docx

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Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
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Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
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Eric

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Sam
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Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

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Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/11/2019 9:00:30 PM
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To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
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Samuel Hernández Quiñones, P.E.
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Lisa Christ
Chief, Targeting and Analysis Branch
Office of Ground Water and Drinking Water
202-564-8354

Message

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Sent: 5/23/2019 9:42:18 AM
To: Eric Burneson [Ex. 6 Personal Privacy (PP)
Subject: Fwd: Revised FRN 5/23/19
Attachments: NPDWR for the Proposed Perchlorate Rule 5-23-19 Ver 0.docx; ATT00001.htm; Redline 5-23-19 Ver0 Perchlorate FRN.docx; ATT00002.htm

Sent from my iPhone

Begin forwarded message:

From: "Hernandez-Quinones, Samuel" <Hernandez.Samuel@epa.gov>
Date: May 23, 2019 at 1:03:20 AM EDT
To: "Burneson, Eric" <Burneson.Eric@epa.gov>
Cc: "Christ, Lisa" <Christ.Lisa@epa.gov>, "Khera, Rajiv" <Khera.Rajiv@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Messier, Dawn" <Messier.Dawn@epa.gov>
Subject: Revised FRN 5/23/19

Hi Eric,
Attached is a clean version of the FRN which incorporates the edits that were offered to OMB earlier tonight. I am also providing here a Redline version that shows the edits the we have incorporated (mainly format) since we sent an updated Version to OMB at 12:53 pm on 5/22/19.

Let me know if you have any comment on the attached files.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

Message

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Sent: 12/21/2018 5:03:01 PM
To: Ross, David P [ross.davidp@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; Campbell, Ann [Campbell.Ann@epa.gov]; Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Wildeman, Anna [wildeman.anna@epa.gov]
Subject: Revised Version - Perchlorate FRN
Attachments: Version-Control Perchlorate Rule FRN 12-20-18.docx

Dave:
Per your request at Wednesday's OGWDW biweekly meeting, attached please find the most recent version of the Proposed Perchlorate Rule Federal Register Notice. Please note that we provided a prior version to Lee and to OGC last week and while they reviewed the document we continued to make edits to improve clarity. Therefore, the attached version is slightly different from the version provided earlier to Lee and OGC and does not reflect their input.

Please let me know if you have any questions or concerns with the attached.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/5/2019 9:25:53 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: Fwd: Perchlorate
Attachments: Perchlorate Proposed NPDWR Redline 4-5-19.docx; ATT00001.htm

FYI Jennifer has a few more edits so use this version.

Sent from my iPhone

Begin forwarded message:

> **From:** "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Date:** April 5, 2019 at 5:24:02 PM EDT
> **To:** "Ross, David P" <ross.davidp@epa.gov>, "Forsgren, Lee" <Forsgren.Lee@epa.gov>
> **Cc:** "Wildeman, Anna" <wildeman.anna@epa.gov>, "Kramer, Jessica L." <kramer.jessical@epa.gov>, "McDonough, Owen" <mcdonough.owen@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>, "Tiago, Joseph" <Tiago.Joseph@epa.gov>, "Aguirre, Janita" <Aguirre.Janita@epa.gov>, "Mejias, Melissa" <mejias.melissa@epa.gov>, "Guilaran, Yu-Ting" <Guilaran.Yu-Ting@epa.gov>
> **Subject: Perchlorate**
>
> Internal/deliberative
>
> Dave & Lee
>
> Before OGWDW formally submits the revised draft Perchlorate Proposed NPDWR package to OW, I wanted you to see a version highlighting the substantive changes we made as a result of our conversations over the past month. Please let us know if you have any recommended changes.
>
> Thanks
> Jennifer
>
> Jennifer L McLain
> Deputy Director
> Office of Ground Water and Drinking Water
> U.S. EPA
> 202-564-4029

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/5/2019 9:16:38 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
CC: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Corr, Elizabeth [Corr.Elizabeth@epa.gov]
Subject: e-files for the perchlorate pkg
Attachments: Perchlorate Draft Action Memo 4-5-19.docx; Transmittal Memo AA to OPEI 4-5-19.docx; Transmittal Memo EB to JM 4-5-19.docx; Transmittal Memo JM to DR 4-5-19.docx

Jennifer: Attached please find updated transmittal memos to reflect the changes in the FRN notice for the perchlorate proposal. Please note that we have not attached the revised economic analysis. We informed OMB, OP and the OW-IO that we would require an additional week to revise this document.
Please let us know if you need any additional information.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel
Sent: Friday, April 05, 2019 3:57 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Revised Memorandums attached.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Friday, April 05, 2019 1:47 PM
To: Khera, Rajiv <Khera.Rajiv@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg

Perchlorate team
Can we review and revise to be made to the other parts of this package to be consistent with the revised notice.
Thanks

From: Mclain, Jennifer
Sent: Friday, April 05, 2019 12:28 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: Use this version - Comments: e-files for the perchlorate pkg

Eric – is your team working on any updates to the package that may be needed to incorporate the changes we made to the draft proposed rule?

From: Tiago, Joseph
Sent: Wednesday, March 06, 2019 1:32 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Hi Sandy,

Thank you for your edits. Your changes have been accepted and two typos corrected as follows:

DR to AW Memo:
Under Impacts: …and administration requirements consisted of the majority of the annual cost.

DR to BB Memo:
This action presents the results of the EPA's economic analysis of the proposed perchlorate regulation and the Agency's conclusion that benefits of the proposed regulation do not justify the costs.

Let me know if you have any questions.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 1:08 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

I think you mean the NPRM – the rule is attached.
If not, let me know.
Sandy

From: Tiago, Joseph
Sent: Wednesday, March 06, 2019 1:05 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fields, Wanda

<Fields.Wanda@epa.gov>
Subject: RE: Use this version - Comments: e-files for the perchlorate pkg

Thanks, Sandy!

Note the EO 12866 file is blank – not sure it was intentional.

We'll get you a revised version of the memos.

Joe.

From: Evalenko, Sandy
Sent: Wednesday, March 6, 2019 12:59 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>
Subject: Use this version - Comments: e-files for the perchlorate pkg
Importance: High

In this version, I also added the San and Rin in the subject line for the Transmittal memo.

Thanks for sending the Perchlorate package. I have a few edits/comments.

1. Thank you for preparing both a transmittal memo and draft action memo. Attached are comments and suggestions.

2. A minor edit regarding the NPRM file name and OMB's requirements. OMB is particular regarding the naming convention. I added the title to the first page of the FRN and changed the title of the Proposed Rule file to

   EO12866_SDWA NPDWR Perchlorate 2040-AF28 NPRM 20190305

3. I removed the first paragraph of the Tribal EO (see below) – which was the 1st paragraph in the old template. I did not change anything else in the body/text of the Tribal EO.

Executive Order 13175, entitled "Consultation and Coordination with Indian Tribal Governments" (65 FR 67249, November 9, 2000), requires the EPA to develop "an accountable process to ensure meaningful and timely input by Tribal officials in the development of regulatory policies that have Tribal implications." The definition of "policies that have Tribal implications" includes regulations that have "substantial direct effects on one or more Indian Tribes, on the relationship between the federal government and the Indian Tribes, or on the distribution of power and responsibilities between the federal government and Indian Tribes." Under Executive Order 13175, the EPA may not issue a regulation that has Tribal implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the federal government provides the funds necessary to pay the direct compliance costs incurred by Tribal governments, or the EPA consults with Tribal officials early in the process of developing the proposed regulation and develops a Tribal summary impact statement.

Please send me the final versions of the memos and I'll print them.

Sandy

From: Lousberg, Macara
Sent: Tuesday, March 05, 2019 7:22 PM
To: Tiago, Joseph <Tiago.Joseph@epa.gov>

Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: e-files for the perchlorate pkg

Thanks Joe. Looping in Sandy.

Did you all get any comments from Anna or Lee?

Sent from my iPhone

Begin forwarded message:

> **From:** "Tiago, Joseph" <Tiago.Joseph@epa.gov>
> **Date:** March 5, 2019 at 5:27:53 PM EST
> **To:** "Lousberg, Macara" <Lousberg.Macara@epa.gov>
> **Cc:** "Burneson, Eric" <Burneson.Eric@epa.gov>, "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>
> **Subject: FW: e-files for the perchlorate pkg**
>
> Hi Macara,
>
> Please find attached the Perchlorate FRN package for review and processing. I'm bringing the hard copy of the package to you shortly.
>
> Let me know if you have any questions.
>
> Regards,
>
> Joe.

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/4/2019 11:34:47 PM
To: Nickerson, William [Nickerson.William@epa.gov]
Subject: Fwd: Revised Perchlorate FRN
Attachments: Perchlorate Proposed NPDWR Redline 4-4-19.docx; ATT00001.htm

FYI on our status. See below

Sent from my iPhone

Begin forwarded message:

> **From:** "Burneson, Eric" <Burneson.Eric@epa.gov>
> **Date:** April 4, 2019 at 6:21:17 PM EDT
> **To:** "Mclain, Jennifer" <Mclain.Jennifer@epa.gov>, "Guilaran, Yu-Ting" <Guilaran.Yu-Ting@epa.gov>
> **Cc:** "'Joe Tiago (Tiago.Joseph@epa.gov)'" <Tiago.Joseph@epa.gov>, "Hernandez-Quinones, Samuel" <hernandez.samuel@epa.gov>, "Khera, Rajiv" <Khera.Rajiv@epa.gov>, "Christ, Lisa" <Christ.Lisa@epa.gov>, "Messier, Dawn" <Messier.Dawn@epa.gov>, "Wehling, Carrie" <Wehling.Carrie@epa.gov>
> **Subject: RE: Revised Perchlorate FRN**
>
> Jennifer: Because we have had issues transmitting multiple files, I am resending this redline document in case it did not come through in the last email.
> Eric
>
> ---
>
> **From:** Burneson, Eric
> **Sent:** Thursday, April 04, 2019 6:17 PM
> **To:** Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
> **Cc:** Joe Tiago (Tiago.Joseph@epa.gov) <Tiago.Joseph@epa.gov>; Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>
> **Subject:** Revised Perchlorate FRN
>
> Jennifer:
> Attached for transmission to the OW IO are revised draft notices for a Proposed National Primary Drinking Water Regulation. The first attachment is a clean version of the revised document and the second is a redline document that shows the changes made since the last OW-IO review.
>
> The changes made to the document include:
> 1. An additional alternative MCLG and MCL of 90 ug/L based upon a 3 IQ point decrement as the point of departure.
> 2. Additional text describing IQ and the significance of IQ decrements at the population level.
> 3. Additional text describing EPA's selection of the proposed MCLG
> 4. Additional presentation of costs and benefits of the new alternative MCLG/MCL
> 5. Additional request for comment on the methodology for deriving the MCLG and alternatives.
>
> The attached materials incorporate the comments that we received from you and from OGC. OGC has concluded that the drafts they reviewed "meets the consent decree obligations." Please let us know if you have any questions or concerns with the attached documents.
>
> Eric Burneson, P.E.

Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/4/2019 10:17:16 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
CC: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: Revised Perchlorate FRN
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190404.docx; Perchlorate Proposed NPDWR Redline 4-4-19.docx

Jennifer:
Attached for transmission to the OW IO are revised draft notices for a Proposed National Primary Drinking Water Regulation. The first attachment is a clean version of the revised document and the second is a redline document that shows the changes made since the last OW-IO review.

The changes made to the document include:

1. An additional alternative MCLG and MCL of 90 ug/L based upon a 3 IQ point decrement as the point of departure.
2. Additional text describing IQ and the significance of IQ decrements at the population level.
3. Additional text describing EPA's selection of the proposed MCLG
4. Additional presentation of costs and benefits of the new alternative MCLG/MCL
5. Additional request for comment on the methodology for deriving the MCLG and alternatives.

The attached materials incorporate the comments that we received from you and from OGC. OGC has concluded that the drafts they reviewed "meets the consent decree obligations." Please let us know if you have any questions or concerns with the attached documents.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/4/2019 7:18:24 PM
To: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
Subject: FW: Revised Perchlorate FRN
Attachments: Clean EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190303.docx; Redline EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20190303.docx

FYI

From: Burneson, Eric
Sent: Sunday, March 03, 2019 9:15 AM
To: Ross, David P <ross.davidp@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>
Cc: Kramer, Jessica L. <kramer.jessical@epa.gov>; Wildeman, Anna <wildeman.anna@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Revised Perchlorate FRN

Dave and Lee:
Attached please find files containing the revised Federal Register Notice for the Proposed Perchlorate Drinking Water Regulation. One is a clean and the other a redline strikeout version showing the changes to the document since your

Ex. 5 Deliberative Process (DP)

Please let me know if you have any questions or concerns with the attached materials.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/14/2019 2:17:31 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: Fwd: Paper published on EPA model re Perchlorate
Attachments: Clewell etal (2019) ClO4 BBDR Review RegToxPharm.pdf; ATT00001.htm

Sent from my iPhone

Begin forwarded message:

From: Tracy Mehan <tmehan@awwa.org>
Date: February 14, 2019 at 9:09:51 AM EST
To: Tracy Mehan <tmehan@awwa.org>
Subject: Paper published on EPA model re Perchlorate

You may find this paper of interest re the perchlorate conversations.

The accepted manuscript has been posted and is open access.

Actual is attached and here is the link https://doi.org/10.1016/j.yrtph.2019.01.028

Thank you.

G. Tracy Mehan, III
Executive Director, Government Affairs
American Water Works Association
202-326-6125 (direct)

Attachment

This communication is the property of the American Water Works Association and may contain confidential or privileged information. Unauthorized use of this communication is strictly prohibited and may be unlawful. If you have received this communication in error, please immediately notify the sender by reply email and destroy all copies of the communication and any attachments.

American Water Works Association
Dedicated to the World's Most Important Resource ®

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/4/2019 7:15:14 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
CC: Joe Tiago (Tiago.Joseph@epa.gov) [Tiago.Joseph@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Rodgers-Jenkins, Crystal [Rodgers-Jenkins.Crystal@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
Subject: Transmittal Memos for Perchlorate
Attachments: Transmittal Memo EB to JM 3-4-19.docx; Transmittal Memo JM to DR 3-4-19.docx; Transmittal Memo AA to OPEI 3-4-19.docx; Perchlorate Draft Action Memo 3-4-19.docx

Jennifer and Yu-Ting:
Attached for your review and comment are the transmittal memos we are preparing to facilitate Inter Agency Review of the propose perchlorate drinking water standard. We will be preparing the "blue folder"package to facilitate getting these documents to the Office of Policy for transmission to OMB for review. Please note that we have been informed that OGC concurrence requires senior level approval now and we do not expect to receive that concurrence today. Also a reminder that the Action memo is a draft at this stage of the process to identify the information we intend to highlight for the Administrator when it is transmitted for signature after OMB concludes Inter Agency Review.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/1/2019 1:25:00 AM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: Fwd: Interagency Comments on Draft Perchlorate MCL NPRM (2 of 2)
Attachments: EPA Perchlorate MCL NPRM (DOD).pdf; ATT00001.htm; EPA Perchlorate MCL TSD (CDC).docx; ATT00002.htm; EPA Perchlorate MCL TSD (DOD).pdf; ATT00003.htm; EPA Perchlorate MCL (NASA).docx; ATT00004.htm; EPA Perchlorate MCL (SBA).docx; ATT00005.htm; EPA Perchlorate MCL HRRCA (CDC).docx; ATT00006.htm; EPA Perchlorate MCL HRRCA (DOD).pdf; ATT00007.htm; EPA Perchlorate MCL NPRM (CDC FDA NIH).docx; ATT00008.htm

Sent from my iPhone

Begin forwarded message:

From: "Dorjets, Vlad EOP/OMB" <Ex. 6 Personal Privacy (PP)
To: "Nickerson, William" <Nickerson.William@epa.gov>
Cc: "Burneson, Eric" <Burneson.Eric@epa.gov>
Subject: Interagency Comments on Draft Perchlorate MCL NPRM (2 of 2)

Bill,

Per my previous message, please find attached comments from certain interagency reviewers on EPA's draft proposal setting an MCL for perchlorate.

Vlad

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 10/3/2018 4:16:08 PM
To: Miller, Wynne [Miller.Wynne@epa.gov]
Subject: FW: Follow up from perchlorate meeting
Attachments: Perchlorate Public Comment Report_Panel 2.pdf; MCLG Approaches Vol1 Main ReportCLEAN V2 7-11-18.docx

Here are the exchanges we have had with Nancy and Mary Hanley about perchlorate.

From: Hernandez-Quinones, Samuel
Sent: Wednesday, September 26, 2018 4:37 PM
To: Hanley, Mary <Hanley.Mary@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Follow up from perchlorate meeting

The Peer-Review Reports are available under supporting documents in Docket # EPA-HQ-OW-2016-0439. I am Attaching the Reports as well as the public comment summary for the 2018 Peer Review effort.

https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0439-0006

https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0439-0012

I will get the 2017 summary report to you by tomorrow.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric
Sent: Wednesday, September 26, 2018 4:10 PM
To: Hanley, Mary <Hanley.Mary@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: Re: Follow up from perchlorate meeting

Mary
Lease check with Lisa Christ or Sam Hernandez-Quinones who can get you to these documents
Eric
Sent from my iPhone

On Sep 26, 2018, at 3:34 PM, Hanley, Mary <Hanley.Mary@epa.gov> wrote:

Eric,

On Nancy's behalf I am trying to find the contractor peer review report for the January 2017 peer review and the contractor's public comment summaries for both the January 2017 and January 2018 contractor peer reviews. I may be missing them but I am not seeing them in either dockets 0438 or 0439. Is there a POC who I can reach out to?
Thanks
Mary
564-0316

From: Burneson, Eric
Sent: Tuesday, September 25, 2018 11:35 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Follow up from perchlorate meeting

Nancy:
Thanks for your questions at yesterday's briefing on perchlorate, particularly regarding EPA's analysis linking thyroid hormone level changes to IQ decrements. As we discussed, the origin of this analysis was the recommendation of the Science Advisory Board. The SAB stated "The agency should incorporate the appropriate studies related to ingestion of perchlorate, pharmacokinetics of perchlorate, the effects (dynamics) of perchlorate, and dose-response relationships from all the available literature. In developing the pharmacodynamic aspect of this model, the EPA should take advantage of available data on potential adverse health effects due to thyroid hormone perturbations, regardless of the cause of those perturbations, to document and support parameters used in the model. Accordingly, the SAB concludes that these two streams of information — biology of iodide deficiency and perchlorate inhibition of iodide uptake — are complementary and sufficient for the EPA to consider specific life stage factors in deriving an MCLG for perchlorate."
See https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/d3bb75d4297ca4698525794300522ace!OpenDocument&TableRow=2.3#2 for more information.

Also, you asked about the subsequent peer reviews of the work done to implement the SAB's recommendations. As discussed, we performed these peer reviews in accordance with the Agency's guidance on Contractor Lead Highly Influential Scientific Assessments, which provides the public with opportunities to comment on both the peer reviewers and the draft report. Several of the peer reviewers for the contractor lead peer reviews were also members of the SAB panel. The first peer review focused on the BBDR model's ability to predict thyroid hormone changes associated with perchlorate exposure and the second peer review focused upon the changes made to the BBDR model and the evaluation of epidemiologic studies evaluating the relationship between thyroid changes and neurodevelopmental impacts. We sought input from Federal partners on the peer review charges and they provided comments on the draft reports in the public docket.

The Peer review docket including the peer review reports and the public input can be found at https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0439.

Also attached for your information is the current version of the scientific analysis that responds to the most recent peer review comments. Please let us know if you have any further questions or concerns that you would like to discuss.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 2/12/2018 10:57:51 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]
CC: Bahadori, Tina [Bahadori.Tina@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: FW: Submission of Comments for the IRIS Process Workshop
Attachments: NRC IRIS Feb 9 2018 Comments Final.pdf

Colleagues:
I am sharing a note I received from SBA today which seems focused on IRIS process but which makes reference to Perchlorate.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Bromberg, Kevin L. [mailto:kevin.bromberg@sba.gov]
Sent: Monday, February 12, 2018 10:49 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: James_H_Kim@omb.eop.gov
Subject: FW: Submission of Comments for the IRIS Process Workshop

Hi Eric – see section of NRC comments re: perchlorate towards the end of this letter.

Kevin Bromberg
Assistant Chief Counsel for Environmental Policy
SBA // Office of Advocacy
409 3rd St. SW, Washington, D.C. 20416
kevin.bromberg@sba.gov 202.481.2963
202.205.6964

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 1/26/2018 4:53:38 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: Fwd: Perchlorate Pre-Meeting Peer Review Summary Report
Attachments: Pre-Meeting Comment Report for Perchlorate_Draft 1.23.18.pdf; ATT00001.htm

Sent from my iPhone

Begin forwarded message:

From: "Hafez, Ahmed" <Hafez.Ahmed@epa.gov>
Date: January 26, 2018 at 11:53:03 AM EST
To: "Flowers, Lynn" <Flowers.Lynn@epa.gov>, "Schlosser, Paul" <Schlosser.Paul@epa.gov>, "Lavoie, Emma" <Lavoie.Emma@epa.gov>, "Bussard, David" <Bussard.David@epa.gov>, "Morozov, Viktor" <Morozov.Viktor@epa.gov>, "Kapraun, Dustin" <Kapraun.Dustin@epa.gov>
Cc: "Hernandez-Quinones, Samuel" <Hernandez.Samuel@epa.gov>, "Christ, Lisa" <Christ.Lisa@epa.gov>, "Burneson, Eric" <Burneson.Eric@epa.gov>
Subject: RE: Perchlorate Pre-Meeting Peer Review Summary Report

With attachment this time.

Ahmed M. Hafez, Ph.D.
OW/OGWDW/SRMD/TAB | Office: WJC East 2227Q
hafez.ahmed@epa.gov | phone: 202.564.1944

From: Hafez, Ahmed
Sent: Friday, January 26, 2018 11:52 AM
To: Flowers, Lynn <Flowers.Lynn@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Cc: Samuel Hernandez-Quinones (Hernandez.Samuel@epa.gov) <Hernandez.Samuel@epa.gov>; Lisa Christ (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Perchlorate Pre-Meeting Peer Review Summary Report

Hello all,

Please find attached the latest version of the pre-meeting peer reviewer's comments to include Drs. Carrasco and Emond to complete the set (8 of 8).

Let me know if you have any questions.

Regards,
Ahmed

Ahmed M. Hafez, Ph.D.
OW/OGWDW/SRMD/TAB | Office: WJC East 2227Q
hafez.ahmed@epa.gov | phone: 202.564.1944

Appointment

From: Meiburg, Stan [Meiburg.Stan@epa.gov]
Sent: 7/28/2016 5:06:22 PM
To: Meiburg, Stan [Meiburg.Stan@epa.gov]; Beauvais, Joel [Beauvais.Joel@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Burke, Thomas [Burke.Thomas@epa.gov]; Vaught, Laura [Vaught.Laura@epa.gov]; Mitchell, Stacey [Mitchell.Stacey@epa.gov]; Neugeboren, Steven [Neugeboren.Steven@epa.gov]
CC: Townsend, Clifton [Townsend.Clifton@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Greene, Ashley [Greene.Ashley@epa.gov]; Campbell, Ann [Campbell.Ann@epa.gov]; Threet, Derek [Threet.Derek@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]

Subject: Perchlorate in Drinking Water
Attachments: Perchlorate in Drinking Waterv4 7-28-16.pptx
Location: WJC-N 3412

Start: 8/1/2016 8:30:00 PM
End: 8/1/2016 9:00:00 PM
Show Time As: Busy

Perchlorate in Drinking Waterv4 7-28-16.pptx

Point of Contact for the Meeting: Lisa Christ 202-564-8354
SCt: Denise Anderson, 564-1782

Purpose: To provide background information on EPA's activities related to the development of a National Primary Drinking Water Regulation for Perchlorate and peer review of scientific reports.

Background: In February, 2011 EPA published a determination to regulate perchlorate in drinking water. In 2012, EPA sought recommendations from SAB on how to derive a MCLG for perchlorate in accordance with SDWA. To address SAB recommendations, EPA and FDA scientist worked collaboratively to develop a Biologically Based Dose-Response model (PBPK model) to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate. EPA will conduct an expert peer review of the model, model report and report describing approaches to derive an MCLG in late 2016. EPA will convene a combined peer review process to take advantage of efficiencies and in response to a lawsuit filed by NRDC alleging EPA failed to propose and finalize a NPDWR for perchlorate by the statutory deadline.

EPA Staff (Required): Stan Meiburg, Joel Beauvais, Peter Grevatt, Eric Burneson, Lisa Christ, Daniel Olson, Tom Burke, Laura Vaught

EPA Staff (Optional): Clifton Townsend, Samuel Hernandez-Quinones, Russ Perkinson, Erik Helm, Jessica Georges. Ashley Greene, Ann Campbell