Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/10/2017 12:50:06 PM
To: Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB Ex. 6 Personal Privacy (PP)]; Vlad Dorjets Ex. 6 Personal Privacy (PP)
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim Ex. 6 Personal Privacy (PP)]; Barringer, Jody M. EOP/OMB Ex. 6 Personal Privacy (PP) Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Seale, Viktoria Z. EOP/CEQ Ex. 6 Personal Privacy (PP) Bahadori, Tina [Bahadori.Tina@epa.gov]; Ex. 6 DOD (PP) Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN) [Emily.Adamo@em.doe.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]

Subject: Canceled: Interagency Perchlorate Peer Review Briefing with EPA
Location: teleconference Ex. 6 Personal Privacy (PP)

Start: 7/10/2017 2:00:00 PM
End: 7/10/2017 3:00:00 PM
Show Time As: Free

Importance: High

Appointment

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 7/10/2018 7:05:20 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Kim, Jim H. EOP/OMB; Ex. 6 Personal Privacy EOP (PP)

Subject: TWG - Perchlorate

Start: 7/11/2018 2:00:00 PM
End: 7/11/2018 2:30:00 PM
Show Time As: Busy

Great: I will speak to you then.

From: Kim, Jim H. EOP/OMB [mailto: Ex. 6 Personal Privacy EOP (PP)
Sent: Tuesday, July 10, 2018 3:04 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: TWG - Perchlorate

Hi Eric,

Sure – can I call around 10AM?

Jim

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, July 10, 2018 2:57 PM
To: Kim, Jim H. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >
Subject: FW: TWG - Perchlorate

Jim:
Can we have a conversation about expectations for tomorrow's call? I am available tomorrow morning. My number is below.

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: Wennerberg, Linda S. (HQ-LD020) [mailto:linda.s.wennerberg@nasa.gov]
Sent: Tuesday, July 10, 2018 2:21 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; James_H_Kim Ex. 6 Personal Privacy EOP (PP); Ex. 6 DOD (PP) Ex. 6 DOD (PP) Seifert, Robert <Robert.Seifert@EM.Doe.Gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Waqar, Tayyaba <tayyaba.waqar@sba.gov>; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP < Ex. 6 Personal Privacy EOP (PP) >; Schwab, Margo EOP/OMB < Ex. 6 Personal Privacy EOP (PP) ; Laity, Jim A.

EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Szabo, Aaron L. EOP/CEQ < Ex. 6 Personal Privacy EOP (PP) >; Barringer, Jody M. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Falk Curtin, Edna T. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Gamache, Christopher D. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Dorjets, Vlad EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fine, Leah R. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >
Subject: RE: TWG - Perchlorate

All
Thanks to Jim for setting this meeting up. Also thanks to Eric Burneson for pointing us to the EPA docket and the peer review report.

Are there any other EPA documents or drafts available for interagency review prior to the meeting? If so, I request the EPA folks please share them so that we can be better informed.

Many thanks. Looking forward to the discussion on Wednesday.

Linda

Linda S. Wennerberg, Ph.D.
Environmental Management Division
NASA Headquarters
MS-2T89
300 E Street SW
Washington, DC 20546-0001

Tel: 202/358-4558
Cell: Ex. 6 Personal Privacy (PP)
Fax: 202/358-3948
linda.s.wennerberg@nasa.gov

From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Monday, July 09, 2018 5:03 PM
To: James_H_Kim Ex. 6 Personal Privacy (PP) Ex. 6 DOD (PP) Wennerberg, Linda S. (HQ-LD020) <linda.s.wennerberg@nasa.gov>; Seifert, Robert <Robert.Seifert@EM.Doe.Gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Waqar, Tayyaba <tayyaba.waqar@sba.gov>; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP < Ex. 6 Personal Privacy EOP (PP) >; Schwab, Margo EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Laity, Jim A. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Szabo, Aaron L. EOP/CEQ < Ex. 6 Personal Privacy EOP (PP) >; Barringer, Jody M. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Falk Curtin, Edna T. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Gamache, Christopher D. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Dorjets, Vlad EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Fine, Leah R. EOP/OMB < Ex. 6 Personal Privacy EOP (PP) >
Subject: RE: TWG - Perchlorate

Jim:
Thank you for setting up this meeting. Please note that the external peer review was completed in March, 2018. The peer review report is attached and is also in the docket at >https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0439<. We look forward to speaking with the technical work group about this analysis and the steps EPA is taking to address peer review comments.

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

-----Original Appointment-----
From: Kim, Jim H. EOP/OMB [mailto: Ex. 6 Personal Privacy EOP (PP)
Sent: Monday, July 09, 2018 11:06 AM
To: Ex. 6 DOD (PP) Wennerberg, Linda S. (HQ-LD020); Seifert, Robert; Burneson, Eric; Grevatt, Peter; Waqar, Tayyaba; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP; Schwab, Margo EOP/OMB; Laity, Jim A. EOP/OMB; Szabo, Aaron L. EOP/CEQ; Barringer, Jody M. EOP/OMB; Falk Curtin, Edna T. EOP/OMB; Gamache, Christopher D. EOP/OMB; Dorjets, Vlad EOP/OMB; Mclain, Jennifer; Fine, Leah R. EOP/OMB
Subject: TWG - Perchlorate
When: Wednesday, July 11, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Conference Call

Dear Technical Working Group:

I am scheduling this conference call so that EPA can update us on their actions on regulating perchlorate in water. The external peer review of the scientific documents was completed last fall, and we have not had a recent update on the status of this activity.

Call-in Number: Ex. 6 Personal Privacy (PP)
Participants: Ex. 6 Personal Privacy (PP)

Let me know if you have questions.

Jim

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/28/2017 3:22:00 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Ex. 6 DOD (PP) Robert.Seifert@EM.Doe.Gov; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Margo_Schwab Ex. 6 Personal Privacy EOP (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy EOP (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick [Suzanne.Fitzpatrick@fda.hhs.gov]; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) kevin.bromberg@sba.gov; Ex. 6 DOD (PP) Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP) Mary.B.Neumayr@ Ex. 6 Personal Privacy EOP (PP) Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP) James_H_Kim Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP); Ex. 6 DOD (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy EOP (PP); Vlad Dorjets Ex. 6 Personal Privacy EOP (PP)
CC: Kabadi, Shruti [Shruti.Kabadi@fda.hhs.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Chin, Teung [Teung.Chin@ARS.USDA.GOV]

Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA
Location: EPA Headquarters East Bldg, 1201 Constitution Avenue NW, Room 2123

Start: 8/9/2017 7:00:00 PM
End: 8/9/2017 9:00:00 PM
Show Time As: Busy

EPA headquarters "East" building, entrance on Constitution Avenue between 12th & 13th at Federal Triangle, https://www.epa.gov/aboutepa/visiting-epa-headquarters

Will follow up with additional visitor instructions as needed. Conference room 2123 in the East building.

Teleconference Ex. 6 Personal Privacy (PP) access code Ex. 6 Personal Privacy (PP)

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/10/2017 6:00:52 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Margo_Schwab Ex. 6 Personal Privacy EOP (PP)]; Vlad Dorjets Ex. 6 Personal Privacy EOP (PP)
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim Ex. 6 Personal Privacy EOP (PP)]; Barringer, Jody M. EOP/OMB Ex. 6 Personal Privacy EOP (PP)]; Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; Seale, Viktoria Z. EOP/CEQ Ex. 6 Personal Privacy EOP (PP)]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN [Emily.Adamo@em.doe.gov]; Ex. 6 DOD (PP) Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]; Clark, Steve [Steve.Clark@hq.doe.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Lumen, Annie [Annie.Lumen@fda.hhs.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP)]; Dinovi, Michael J [Michael.Dinovi@fda.hhs.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Suzanne_Fitzpatrick [Suzanne.Fitzpatrick@fda.hhs.gov]; Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Nasir, Iqra [nasir.iqra@epa.gov]; Smegal, Deborah [Deborah.Smegal@fda.hhs.gov]

Subject: Interagency Perchlorate Peer Review Briefing with EPA (rescheduled)
Location: teleconference Ex. 6 Personal Privacy (PP) / access code Ex. 6 Personal Privacy (PP)

Start: 7/18/2017 6:00:00 PM
End: 7/18/2017 7:00:00 PM
Show Time As: Busy

Draft agenda:

- Perchlorate BBDR Model Peer Review Outcome
  - Reviewers response to charge
  - EPA's actions on peer review recommendations
- Overview of Revisions to the BBDR Model
- MCLG Approaches
- Next Steps

EPA's recent model and peer review materials:

Ex. 6 Personal Privacy Internal URL (PP)

Revised briefing materials to follow.

Appointment

From: Kim, Jim H. EOP/OMB [redacted]
Sent: 7/9/2018 3:06:31 PM
To: James_H_Kim [redacted] Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Waqar, Tayyaba [tayyaba.waqar@sba.gov]; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP [redacted]; Schwab, Margo EOP/OMB [redacted]; Laity, Jim A. EOP/OMB [redacted]; Szabo, Aaron L. EOP/CEQ [redacted]; Barringer, Jody M. EOP/OMB [redacted]; Falk Curtin, Edna T. EOP/OMB [redacted]; Gamache, Christopher D. EOP/OMB [redacted]; Dorjets, Vlad EOP/OMB [redacted]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fine, Leah R. EOP/OMB [redacted]

Subject: TWG - Perchlorate
Location: Conference Call

Start: 7/11/2018 6:00:00 PM
End: 7/11/2018 7:00:00 PM
Show Time As: Busy

Recurrence: (none)

Dear Technical Working Group:

I am scheduling this conference call so that EPA can update us on their actions on regulating perchlorate in water. The external peer review of the scientific documents was completed last fall, and we have not had a recent update on the status of this activity.

Call-in Number: [redacted]
Participants: [redacted]

Let me know if you have questions.

Jim

Message

From: Morozov, Viktor [Morozov.Viktor@epa.gov]
Sent: 11/1/2017 1:14:03 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Schlosser, Paul [Schlosser.Paul@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Hauchman, Fred [hauchman.fred@epa.gov]
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Hi Eric,
Thank you for contacting Ex. 6 Personal Privacy (PP) Let's wait for Ex. 6 Personal Privacy (PP) respond with a list of questions for Paul and Dustin before scheduling conference call.

-Viktor.

Viktor Morozov, Ph.D.
Chief, Quantitative Risk Methods Group (QRMG)
National Center for Environmental Assessment (NCEA), Washington Division (MC-8623P)
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Dr., Rm 11761
Arlington, Virginia 22202
Office: 703-347-8156
Mobil Ex. 6 Personal Privacy (PP)

From: Burneson, Eric
Sent: Wednesday, November 01, 2017 8:58 AM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Victor et al.
Ex. 6 Personal Privacy (PP) called me back and left a voicemail message stating that Ex. 6 Personal Privacy (PP) s group is interested in asking questions about how to run the BBDR model. She did not have the specific questions but would ask Ex. 6 Personal Privacy (PP) o see if he could come up with a list.

I am inclined to recommend a conference call with Ex. 6 Personal Privacy (PP) group, ask for the questions in advance but note that we may need to follow up afterwards with answers after the call if new questions raised that require internal deliberation.
I will wait for your reply before responding to Ex. 6 Personal Privacy (PP)

From: Burneson, Eric
Sent: Tuesday, October 31, 2017 5:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; 'Christopher_D_Gamache@ Ex. 6 Personal Privacy (PP)
<Christopher_D_Gamache@ Ex. 6 Personal Privacy (PP)
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I have a call into Ex. 6 Personal Privacy (PP) nd would propose a conference call. Would that work for you ?

P.S. I don't think they want us to run the model for them just ask questions about how to run the model.

From: Morozov, Viktor
Sent: Tuesday, October 31, 2017 5:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Hi Eric,
What would be the best way to handle this? A conference call to Ex. 6 Personal Privacy (PP) ? Please see email for Paul.
-Viktor.

Viktor Morozov, Ph.D.
Chief, Quantitative Risk Methods Group (QRMG)
National Center for Environmental Assessment (NCEA), Washington Division (MC-8623P)
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Dr., Rm 11761
Arlington, Virginia 22202
Office: 703-347-8156
Mobile: Ex. 6 Personal Privacy (PP)

From: Schlosser, Paul
Sent: Tuesday, October 31, 2017 4:46 PM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Also copying Dustin:

Depending on what exactly DOD wants, it shouldn't be hard to run some additional simulations with the perchlorate model.

Tomorrow mornin Ex. 6 Personal Privacy (PP) and then the talk that Dustin and I are doing for R5/States meeting in the afternoon, so it will be a little busy, but middle of the day is now clear.

-Paul

From: Bussard, David
Sent: Tuesday, October 31, 2017 4:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I'm passing this on. I don't see attached questions, however.
David

From: Flowers, Lynn
Sent: Tuesday, October 31, 2017 4:11 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hauchman, Fred <hauchman.fred@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Christ, Lisa

<Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Re: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric: I am just about to check out! Interesting request. I suggest that you work with David Bussard to set up a call.
Lynn

Sent from my iPhone

On Oct 31, 2017, at 4:05 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

> Lynn and Fred: Please see the request we just received for assistance answering questions about the BBDR model from DOD. I would like to discuss with you our potential responses to this question. Lynn I recall you are either going out of town or will soon be departing which is why I am including Fred.
>
> I think a call would be appropriate. Who do you recommend be included in the discussion?
>
> Eric
>
> -----Original Message-----
> From: [Ex. 6 Personal Privacy (PP)]
> Sent: Tuesday, October 31, 2017 2:55 PM
> To: Burneson, Eric <Burneson.Eric@epa.gov>
> Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)
>
> CLASSIFICATION: UNCLASSIFIED
>
> Eric,
> While reviewing the report, a question has emerged from our DoD toxicologists. We were wondering if we have a question about the model that could only be answered by someone running a model simulation, could we ask Paul Schlosser to do that? We are trying to get the model running here and answer any questions we have ourselves. However, one of our modelers just left to work for industry so we are a little short-handed right now and we are looking at all options.
>
> Thank you for any help or thoughts on how to address this.
>
> Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Friday, October 6, 2017 4:03 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OME Ex. 6 Personal Privacy (PP) ; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

Margo_Schwab(Ex. 6 Personal Privacy (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy (PP) v; Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy (PP) ; Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick <Suzanne.Fitzpatrick@fda.hhs.gov>; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher <Jeffrey.Fisher@fda.hhs.gov>; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Andrea_L_Grossman Ex. 6 Personal Privacy (PP) y; kevin.bromberg@sba.gov; F Ex. 6 Personal Privacy (PP)
Christopher_D_Gamache Ex. 6 Personal Privacy (PP) Mary.B.Neumayr Ex. 6 Personal Privacy (PP)
Jennifer_M_Le Ex. 6 Personal Privacy (PP) ; James_H_Kim Ex. 6 Personal Privacy (PP) ; Ex. 6 Personal Privacy (PP)
Viktoria.Z.Seale Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy (PP) Vlad Ex. 6 Personal Privacy (PP) ; Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ Ex. 6 Personal Privacy (PP) ; Corrales, Mark <Corrales.Mark@epa.gov>; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; DCRoomEast2123/DC-ICC-OW-OGWDW <DCRoomEast2123@epa.gov>; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB Ex. 6 Personal Privacy (PP) ; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

Margo_Schwab Ex. 6 Personal Privacy (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White@ Ex. 6 Personal Privacy (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin@ Ex. 6 Personal Privacy (PP) ; Annie.Lumen@fda.hhs.gov; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Andrea_L_Grossman@ Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)
Christopher_D_Gamache@ Ex. 6 Personal Privacy (PP) Mary.B.Neumayr Ex. 6 Personal Privacy (PP)
Jennifer_M_Lee Ex. 6 Personal Privacy (PP) ; Ex. 6 Personal Privacy (PP) ; Viktoria.Z.Seale Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP); Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy (PP); Vlad Dorjets Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ Ex. 6 Personal Privacy (PP) gov>; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB Ex. 6 Personal Privacy (PP); Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Margo_Schwab@ Ex. 6 Personal Privacy (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy (PP) Annie.Lumen@fda.hhs.gov; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Andrea_L_Grossman Ex. 6 Personal Privacy (PP); Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Christopher_D_Gamache Ex. 6 Personal Privacy (PP) Mary.B.Neumayr Ex. 6 Personal Privacy (PP) Jennifer_M_Lee@ Ex. 6 Personal Privacy (PP) Viktoria.Z.Seale Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy (PP) Vlad Dorjets Ex. 6 Personal Privacy (PP) Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ < Ex. 6 Personal Privacy (PP) >; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: [Non-DoD Source] EPA Perchlorate Peer Review Comment Deadlines

Federal Partners:

As we have discussed previously, EPA currently has two pending requests for comment related to the perchlorate peer review.

1. The deadline for comments on the charge question and potential peer reviewers is today. The comment deadline for this request remains unchanged. Note that you have the option of sending your comments directly to me via email.

2. The current deadline for the comments on the report is October 30, 2017. EPA will be extending the deadline for the comments on the Draft Report and Model by 21 days. We expect to publish a comment deadline extension (to Nov. 20) in the Federal Register next week.

Thank you for your continued input 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

CLASSIFICATION: UNCLASSIFIED

Message

From: Schlosser, Paul [Schlosser.Paul@epa.gov]
Sent: 11/1/2017 1:10:54 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]
CC: Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Hauchman, Fred [hauchman.fred@epa.gov]
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Something it would be good to know in advance is if they are trying to work with the acslX version or the R/MCSim version of the model. They are essentially identical, although how you do things in each software is different and the formatting of plots will differ. So only one needs to be implemented.

-Paul

From: Burneson, Eric
Sent: Wednesday, November 01, 2017 8:58 AM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Victor et al.
Ex. 6 Personal Privacy (PP) called me back and left a voicemail message stating that Ex. 6 Personal Privacy (PP) group is interested in asking questions about how to run the BBDR model. She did not have the specific questions but would ask Ex. 6 Personal Privacy (PP) to see if he could come up with a list.

I am inclined to recommend a conference call with Ex. 6 Personal Privacy (PP) group, ask for the questions in advance but note that we may need to follow up afterwards with answers after the call if new questions raised that require internal deliberation.
I will wait for your reply before responding to Ex. 6 Personal Privacy (PP)

From: Burneson, Eric
Sent: Tuesday, October 31, 2017 5:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; 'Christopher_D_Gamache@Ex. 6 Personal Privacy (PP) <Christopher_D_Gamache@Ex. 6 Personal Privacy (PP)
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I have a call into [redacted] and would propose a conference call. Would that work for you ?

P.S. I don't think they want us to run the model for them just ask questions about how to run the model.

From: Morozov, Viktor
Sent: Tuesday, October 31, 2017 5:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David

<Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Hi Eric,
What would be the best way to handle this? A conference call to Ex. 6 Personal Privacy (PP)? Please see email for Paul.
-Viktor.

Viktor Morozov, Ph.D.
Chief, Quantitative Risk Methods Group (QRMG)
National Center for Environmental Assessment (NCEA), Washington Division (MC-8623P)
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Dr., Rm 11761
Arlington, Virginia 22202
Office: 703-347-8156
Mobile: Ex. 6 Personal Privacy (PP)

From: Schlosser, Paul
Sent: Tuesday, October 31, 2017 4:46 PM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Also copying Dustin:

Depending on what exactly DOD wants, it shouldn't be hard to run some additional simulations with the perchlorate model.

Tomorrow morning Ex. 6 Personal Privacy (PP) and then the talk that Dustin and I are doing for R5/States meeting in the afternoon, so it will be a little busy, but middle of the day is now clear.

-Paul

From: Bussard, David
Sent: Tuesday, October 31, 2017 4:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I'm passing this on. I don't see attached questions, however.
David

From: Flowers, Lynn
Sent: Tuesday, October 31, 2017 4:11 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hauchman, Fred <hauchman.fred@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Re: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric: I am just about to check out! Interesting request. I suggest that you work with David Bussard to set up a call.
Lynn

Sent from my iPhone

On Oct 31, 2017, at 4:05 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

Lynn and Fred: Please see the request we just received for assistance answering questions about the BBDR model from DOD. I would like to discuss with you our potential responses to this question. Lynn I recall you are either going out of town or will soon be departing which is why I am including Fred.

I think a call would be appropriate. Who do you recommend be included in the discussion?

Eric

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Tuesday, October 31, 2017 2:55 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

Eric,
While reviewing the report, a question has emerged from our DoD toxicologists. We were wondering if we have a question about the model that could only be answered by someone running a model simulation, could we ask Paul Schlosser to do that? We are trying to get the model running here and answer any questions we have ourselves. However, one of our modelers just left to work for industry so we are a little short-handed right now and we are looking at all options.

Thank you for any help or thoughts on how to address this.
Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Friday, October 6, 2017 4:03 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Johnson, Ann

<Johnson.Ann@epa.gov>; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP); Robert.Seifert@EM.Doe.Gov; August, Lisa L.
EOP/OMB Ex. 6 Personal Privacy (PP); Letitia.O'Conor@em.doe.gov;
Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Brannon,
Ex. 6 Personal Privacy (PP)
Margo_Schwab@or Gareth.Buckland@em.doe.gov;
Kamela_G._White@ ov; Sarah.Jensen@Hq.Doe.Gov;
Jody_M._Barringer(Ex. 6 Personal Privacy (PP) ov; Michael.Dinovi@fda.hhs.gov;
Edna_F._Curtin@or Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick
<Suzanne.Fitzpatrick@fda.hhs.gov>; Eileen.Abt@fda.hhs.gov; Apri
l.Kluever@fda.hhs.gov; Jeff Fisher <Jeffrey.Fisher@fda.hhs.gov>; Steve.Clark@hq.doe.gov;
Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) kevin.bromberg@sba.gov;
Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP); Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP); Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov;
Gareth.Buckland@NNSA.DOE.Gov; J Ex. 6 Personal Privacy (PP); Vlad
Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Kabadi, Shruti
<Shruti.Kabadi@fda.hhs.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Chin, Teung
<Teung.Chin@ARS.USDA.GOV>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <St
rong.Jamie@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hafez, Ahmed
<Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Kunickis, Sheryl - OSEC
<Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
Ex. 6 Personal Privacy (PP)>; Corrales, Mark <Corrales.Mark@epa.gov>; Domesle,
Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; DCRoomEast2123/DC-ICC-OW-
OGWDW <DCRoomEast2123@epa.gov>; Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP); Robert.Seifert@EM.Doe.Gov; August, Lisa L.
EOP/OMB Ex. 6 Personal Privacy (PP) v>; Letitia.O'Conor@em.doe.gov;
Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP)
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Margo_Schwab@o reth.Buckland@em.doe.gov;
Kamela_G._White(Ex. 6 Personal Privacy (PP) Sarah.Jensen@Hq.Doe.Gov;
Jody_M._Barringe ; Michael.Dinovi@fda.hhs.gov Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Annie.Lumen@fda.hhs.gov; Eileen.Abt@fda.hhs.gov;
April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)

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Ex. 6 Personal Privacy (PP) Mark.Wirtz@fda.hhs.gov;
Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity
< Ex. 6 Personal Privacy (PP) Vlad Dorjets Ex. 6 Personal Privacy (PP)
< Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Chin, Teung
<Teung.Chin@ARS.USDA.GOV>; Kunickis, Sheryl - OSEC
<Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
<Michael_C_Jensen@ Ex. 6 Personal Privacy (PP)

.gov>; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; Ex. 6 Personal Privacy (PP)
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Ex. 6 Personal Privacy (PP) Annie.Lumen@fda.hhs.gov; Eileen.Abt@fda.hhs.gov;
April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)
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Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy (PP) ; Vlad
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<Shruti.Kabadi@fda.hhs.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Kunickis,
Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
Ex. 6 Personal Privacy (PP) ; Domesle, Alexander - ARS
<Alexander.Domesle@ARS.USDA.GOV>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: [Non-DoD Source] EPA Perchlorate Peer Review Comment Deadlines

Federal Partners:

As we have discussed previously, EPA currently has two pending requests for comment related to the perchlorate peer review.

1. The deadline for comments on the charge question and potential peer reviewers is today. The comment deadline for this request remains unchanged. Note that you have the option of sending your comments directly to me via email.

2. The current deadline for the comments on the report is October 30, 2017. EPA will be extending the deadline for the comments on the Draft Report and Model by 21 days. We expect to publish a comment deadline extension (to Nov. 20) in the Federal Register next week.

Thank you for your continued input 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

CLASSIFICATION: UNCLASSIFIED

Message

From: Bussard, David [Bussard.David@epa.gov]
Sent: 10/31/2017 10:07:02 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Well, there is that.....

By the way, congrats on the complement from EDF about the transparency of clarity of the perchlorate materials.

-----Original Message-----
From: Burneson, Eric
Sent: Tuesday, October 31, 2017 5:54 PM
To: Bussard, David <Bussard.David@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Except when I add OMB by mistake

-----Original Message-----
From: Bussard, David
Sent: Tuesday, October 31, 2017 5:53 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Reply all is fine.

-----Original Message-----
From: Burneson, Eric
Sent: Tuesday, October 31, 2017 5:32 PM
To: Bussard, David <Bussard.David@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Thanks Dave: I will get a sense of the questions from Ex. 6 Personal Privacy (PP) when I hear back and we can go from there. I expect that we will need to go with the two step approach. I will circle back when I hear from them. Also let me know how you want me to communicate with others in NCEA (I just replied to an email from Victor on this same question).

-----Original Message-----
From: Bussard, David
Sent: Tuesday, October 31, 2017 5:23 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric,

If the questions are substantive and would require thought as to how to best answer, written questions allows some pre-scrimmaging of answers.
If they are "how to get the model running", written questions are likely very inefficient.

But, if time is of the essence (say, if they are up against a deadline) or asking for written questions will damage relations with DoD, we can always suggest that we take this in two steps, and do a call to find out what their questions are, and reserve the right to go off-line and think about how best to answer them.

David

-----Original Message-----
From: Burneson, Eric
Sent: Tuesday, October 31, 2017 4:24 PM
To: Bussard, David <Bussard.David@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

They did not send a list of questions, I have a call into Ex. 6 Personal Privacy (PP) to clarify what they are asking. What is your preference? Written Q&A or set up a conference call?

-----Original Message-----
From: Bussard, David
Sent: Tuesday, October 31, 2017 4:23 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric,

Did DoD send a list of questions? Or, are they just saying they want a call and to discuss the questions on the call?

David

-----Original Message-----
From: Burneson, Eric
Sent: Tuesday, October 31, 2017 4:06 PM
To: Flowers, Lynn <Flowers.Lynn@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Cc: Bussard, David <Bussard.David@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Lynn and Fred: Please see the request we just received for assistance answering questions about the BBDR model from DOD. I would like to discuss with you our potential responses to this question. Lynn I recall you are either going out of town or will soon be departing which is why I am including Fred.

I think a call would be appropriate. Who do you recommend be included in the discussion?

Eric

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Tuesday, October 31, 2017 2:55 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

Eric,
While reviewing the report, a question has emerged from our DoD toxicologists. We were wondering if we have a question about the model that could only be answered by someone running a model simulation, could we ask Paul Schlosser to do that? We are trying to get the model running here and answer any questions we have ourselves. However, one of our modelers just left to work for industry so we are a little short-handed right now and we are looking at all options.

Thank you for any help or thoughts on how to address this.
Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Friday, October 6, 2017 4:03 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB Ex. 6 Personal Privacy (PP); Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Margo_Schwab Ex. 6 Personal Privacy (PP); Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy (PP); Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy (PP); Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy (PP); Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick <Suzanne.Fitzpatrick@fda.hhs.gov>; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff.Fisher <Jeffrey.Fisher@fda.hhs.gov>; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Andrea L. Grossman Ex. 6 Personal Privacy (PP); kevin.bromberg@sba.gov; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Christopher_D_Gamache Ex. 6 Personal Privacy (PP); Mary.B.Neumayr Ex. 6 Personal Privacy (PP); Jennifer_M_Lee Ex. 6 Personal Privacy (PP); James_H_Kim@ Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Viktoria.Z.Seale Ex. 6 Personal Privacy (PP); Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy (PP); Vlad Dorjets Ex. 6 Personal Privacy (PP)

Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <St rong.Jamie@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ [redacted]; Corrales, Mark <Corrales.Mark@epa.gov>; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; DCRoomEast2123/DC-ICC-OW-OGWDW <DCRoomEast2123@epa.gov>; [redacted]; Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB [redacted]; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; [redacted]
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[redacted]

[redacted] Christopher_D_Gamache [redacted]; Mary.B.Neumayr [redacted]; Jennifer_M_Lee [redacted]; [redacted] Viktoria.Z.Seale [redacted]; [redacted]; Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity [redacted]; Vlad Dorjets [redacted]; Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ <M [redacted]; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; [redacted] Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB [redacted] Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; [redacted]
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[redacted] [redacted]
[redacted]; Andrea_L_Grossman [redacted]; [redacted]
[redacted]; Christopher_D_Gamache [redacted]; Mary.B.Neumayr [redacted]; Jennifer_M_Lee [redacted] [redacted] Viktoria.Z.Seale [redacted] [redacted]
[redacted]; Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity [redacted]; Vlad Dorjets [redacted]; Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ [redacted]; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: [Non-DoD Source] EPA Perchlorate Peer Review Comment Deadlines

Federal Partners:

As we have discussed previously, EPA currently has two pending requests for comment related to the perchlorate peer review.

1. The deadline for comments on the charge question and potential peer reviewers is today. The comment deadline for this request remains unchanged. Note that you have the option of sending your comments directly to me via email.

2. The current deadline for the comments on the report is October 30, 2017. EPA will be extending the deadline for the comments on the Draft Report and Model by 21 days. We expect to publish a comment deadline extension (to Nov. 20) in the Federal Register next week.

Thank you for your continued input 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

CLASSIFICATION: UNCLASSIFIED

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/10/2017 6:00:52 PM
To: Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Margo_Schwab(Ex. 6 Personal Privacy EOP (PP)]; Vlad Dorjets [Ex. 6 Personal Privacy EOP (PP)]
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim(Ex. 6 Personal Privacy EOP (PP)]; Barringer, Jody M. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; Ex. 6 DOD (PP) ; Ex. 6 DOD (PP) Seale, Viktoria Z. EOP/CEQ [Ex. 6 Personal Privacy EOP (PP)] Bahadori, Tina [Bahadori.Tina@epa.gov]; Ex. 6 DOD (PP) Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN [Emily.Adamo@em.doe.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) ; Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]; Buckland, Gareth [Gareth.Buckland@NNSA.DOE.Gov]; Clark, Steve [Steve.Clark@hq.doe.gov]; Neumayr, Mary B. EOP/CEQ [Ex. 6 Personal Privacy EOP (PP)]

Subject: Interagency Perchlorate Peer Review Briefing with EPA (rescheduled)
Location: teleconference(Ex. 6 Personal Privacy (PP)) / access code(Ex. 6 Personal Privacy (PP))

Start: 7/18/2017 6:00:00 PM
End: 7/18/2017 7:00:00 PM
Show Time As: Tentative

Draft agenda:

- Perchlorate BBDR Model Peer Review Outcome
  - Reviewers response to charge
  - EPA's actions on peer review recommendations
- Overview of Revisions to the BBDR Model
- MCLG Approaches
- Next Steps

EPA's recent model and peer review materials:

Ex. 6 Personal Privacy Internal URL (PP)

Revised briefing materials to follow.

Message

From: Bussard, David [Bussard.David@epa.gov]
Sent: 10/31/2017 9:11:59 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Morozov, Viktor [Morozov.Viktor@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric,

It would be useful to find out from DoD what their questions are in advance and then go from there.

Do you want to do that?

David

From: Morozov, Viktor
Sent: Tuesday, October 31, 2017 5:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Hi Eric,
What would be the best way to handle this? A conference call to Ex. 6 Personal Privacy (PP) Please see email for Paul.
-Viktor.

Viktor Morozov, Ph.D.
Chief, Quantitative Risk Methods Group (QRMG)
National Center for Environmental Assessment (NCEA), Washington Division (MC-8623P)
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Dr., Rm 11761
Arlington, Virginia 22202
Office: 703-347-8156
Mobile: Ex. 6 Personal Privacy (PP)

From: Schlosser, Paul
Sent: Tuesday, October 31, 2017 4:46 PM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Also copying Dustin:

Depending on what exactly DOD wants, it shouldn't be hard to run some additional simulations with the perchlorate model.

Tomorrow morning I have a dentist appointment at 8 am (check-up), and then the talk that Dustin and I are doing for R5/States meeting in the afternoon, so it will be a little busy, but middle of the day is now clear.

-Paul

From: Bussard, David
Sent: Tuesday, October 31, 2017 4:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I'm passing this on. I don't see attached questions, however.
David

From: Flowers, Lynn
Sent: Tuesday, October 31, 2017 4:11 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hauchman, Fred <hauchman.fred@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Re: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric: I am just about to check out! Interesting request. I suggest that you work with David Bussard to set up a call.
Lynn

Sent from my iPhone

On Oct 31, 2017, at 4:05 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

> Lynn and Fred: Please see the request we just received for assistance answering questions about the BBDR model from DOD. I would like to discuss with you our potential responses to this question. Lynn I recall you are either going out of town or will soon be departing which is why I am including Fred.
>
> I think a call would be appropriate. Who do you recommend be included in the discussion?
>
> Eric
>
> -----Original Message-----
> From: Ex. 6 Personal Privacy (PP)
> Sent: Tuesday, October 31, 2017 2:55 PM
> To: Burneson, Eric <Burneson.Eric@epa.gov>
> Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)
>
> CLASSIFICATION: UNCLASSIFIED
>
> Eric,
> While reviewing the report, a question has emerged from our DoD toxicologists. We were wondering if we have a question about the model that could only be answered by someone running a model simulation, could we ask Paul Schlosser to do that? We are trying to get the model running here and answer any questions we have ourselves. However, one of our modelers just left to work for industry so we are a little short-handed right now and we are looking at all options.
>
> Thank you for any help or thoughts on how to address this.
> Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Friday, October 6, 2017 4:03 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Ex. 6 Personal Privacy (PP) <Ex. 6 Personal Privacy (PP)>; Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB <Ex. 6 Personal Privacy (PP)>; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP)

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Margo_Schwab Ex. 6 Personal Privacy (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy (PP) Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick <Suzanne.Fitzpatrick@fda.hhs.gov>; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher <Jeffrey.Fisher@fda.hhs.gov>; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)
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<Ex. 6 Personal Privacy (PP)>; Ex. 6 Personal Privacy (PP) kevin.bromberg@sba.gov;
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Ex. 6 Personal Privacy (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity <Ex. 6 Personal Privacy (PP)>; Vlad Dorjets (Ex. 6 Personal Privacy (PP)) Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Kunickis, Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ <Ex. 6 Personal Privacy (PP)>; Corrales, Mark <Corrales.Mark@epa.gov>; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; DCRoomEast2123/DC-ICC-OW-OGWDW <DCRoomEast2123@epa.gov>; Ex. 6 Personal Privacy (PP)
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April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 Personal Privacy (PP)
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Jennifer_M_Lee Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Viktoria.Z.Seale@ Ex. 6 Personal Privacy (PP); Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)>; Mark.Wirtz@fda.hhs.gov;
Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity
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Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
Ex. 6 Personal Privacy (PP); Domesle, Alexander - ARS
<Alexander.Domesle@ARS.USDA.GOV>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: [Non-DoD Source] EPA Perchlorate Peer Review Comment Deadlines

Federal Partners:

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1. The deadline for comments on the charge question and potential peer reviewers is today. The comment deadline for this request remains unchanged. Note that you have the option of sending your comments directly to me via email.

2. The current deadline for the comments on the report is October 30, 2017. EPA will be extending the deadline for the comments on the Draft Report and Model by 21 days. We expect to publish a comment deadline extension (to Nov. 20) in the Federal Register next week.

Thank you for your continued input 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

CLASSIFICATION: UNCLASSIFIED

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/10/2017 12:50:06 PM
To: Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Ex. 6 Personal Privacy (PP)]; Vlad Dorjets [Ex. 6 Personal Privacy (PP)]
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim([Ex. 6 Personal Privacy (PP)]y; Barringer, Jody M. EOP/OMB [Ex. 6 Personal Privacy (PP)]; Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; [Ex. 6 DOD (PP)] [Ex. 6 DOD (PP)] Seale, Viktoria Z. EOP/CEQ [Ex. 6 Personal Privacy (PP)] Bahadori, Tina [Bahadori.Tina@epa.gov]; [Ex. 6 DOD (PP)] Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN) [Emily.Adamo@em.doe.gov]; [Ex. 6 DOD (PP)] [Ex. 6 DOD (PP)] Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]

Subject: Canceled: Interagency Perchlorate Peer Review Briefing with EPA
Location: teleconference [Ex. 6 Personal Privacy (PP)], access code [Ex. 6 Personal Privacy (PP)]

Start: 7/10/2017 2:00:00 PM
End: 7/10/2017 3:00:00 PM
Show Time As: Free

Importance: High

Margo & Vlad – please share with other interagency partners. Materials to follow.

Message

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/7/2017 12:51:07 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]
Subject: RE: Interagency Perchlorate Peer Review Briefing with EPA

7/12 was not feasible for OMB. Let me know what other dates/times you can suggest.

From: Christ, Lisa
Sent: Thursday, July 06, 2017 5:47 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: RE: Interagency Perchlorate Peer Review Briefing with EPA

Hi Caryn,
I spoke with Eric and we won't be ready for this briefing on Monday. We're revising the presentation and need to coordinate with ORD. Is July 12th still a possibility? If not, we'll need to look at dates later than that. Also please include Tina Bahadori from ORD on the invitation.
Thank you in advance –
Lisa

-----Original Appointment-----
From: Muellerleile, Caryn
Sent: Thursday, July 06, 2017 2:03 PM
To: Muellerleile, Caryn; Hafez, Ahmed; Strong, Jamie; Mclain, Jennifer; Grevatt, Peter; Burneson, Eric; Olson, Daniel; Christ, Lisa; Margo EOP/OMB; Vlad Dorjets
Cc: Behl, Betsy; OP ADP Calendar; Nurse, Leanne; Johnson, Ann; Flowers, Lynn; Schlosser, Paul; Huff, Lisa; James H Kim Ex. 6 Personal Privacy (PP); Barringer, Jody M. EOP/OMB; Abt, Eileen; Morozov, Viktor; Bussard, David; Lavoie, Emma; Moore, Beth; Ex. 6 DOD (PP)
Subject: Interagency Perchlorate Peer Review Briefing with EPA
When: Monday, July 10, 2017 10:00 AM-11:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: teleconference Ex. 6 DOD (PP)

Margo & Vlad – please share with other interagency partners. Materials to follow.

Perchlorate Briefing 7/18/2017

EPA Invitees

Hafez, Ahmed <Hafez.Ahmed@epa.gov>;

Strong, Jamie <Strong.Jamie@epa.gov>;

Mclain, Jennifer <Mclain.Jennifer@epa.gov>;

Grevatt, Peter <Grevatt.Peter@epa.gov>;

Burneson, Eric <Burneson.Eric@epa.gov>;

Olson, Daniel <Olson.Daniel@epa.gov>;

Christ, Lisa <Christ.Lisa@epa.gov>;

Behl, Betsy <Behl.Betsy@epa.gov>;

Nurse, Leanne <Nurse.Leanne@epa.gov>;

Johnson, Ann <Johnson.Ann@epa.gov>;

Flowers, Lynn <Flowers.Lynn@epa.gov>;

Schlosser, Paul <Schlosser.Paul@epa.gov>;

Huff, Lisa <Huff.Lisa@epa.gov>;

Forsgren, Lee <Forsgren.Lee@epa.gov>;

Morozov, Viktor <Morozov.Viktor@epa.gov>;

Bussard, David <Bussard.David@epa.gov>;

Lavoie, Emma <Lavoie.Emma@epa.gov>;

Bahadori, Tina <Bahadori.Tina@epa.gov>;

Miller, Gregory <Miller.Gregory@epa.gov>;

Kapraun, Dustin <Kapraun.Dustin@epa.gov>;

Evalenko, Sandy <Evalenko.Sandy@epa.gov>

OMB & EOP Invitees

Margo EOP/ON

Vlad Dorjets <V

[HYPERLINK "r

Barringer, Jody M.

Seale, Viktoria Z. E

Neumayr, Mary B.

Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

Grossman, Andrea L. Ex. 6 Personal Privacy (PP)

HHS

Abt, Eileen <Eileen.Abt@fda.hhs.gov>;

Kluever, April <April.Kluever@fda.hhs.gov>;

Wirtz, Mark S <Mark.Wirtz@fda.hhs.gov>;

Gavelek, Alexandra <Alexandra.Gavelek@fda.hhs.gov>;

Lumen, Annie <Annie.Lumen@fda.hhs.gov>;

Dinovi, Michael J <Michael.Dinovi@fda.hhs.gov>;

Fitzpatrick, Suzanne <Suzanne.Fitzpatrick@fda.hhs.gov>;

DOE

Moore, Beth <Beth.Moore@em.doe.gov>;

Adamo, Emily (INTERN <Emily.Adamo@em.doe.gov>;

Buckland, Gareth <Gareth.Buckland@NNSA.DOE.Gov>;

Clark, Steve <Steve.Clark@hq.doe.gov>;

Seifert, Robert <Robert.Seifert@EM.Doe.Gov>;

OTHER FEDERAL

Ex. 6 DOD (PP)

kevin.bromberg@sba.gov;

Wennerberg, Linda S. (HQ-LD020) <linda.s.wennerberg@nasa.gov>;

Ex. 6 DOD (PP)

Message

From: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP)
Sent: 7/27/2017 3:55:15 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Another High Quality Perchlorate Study

FYI

From: Bromberg, Kevin L. [mailto:kevin.bromberg@sba.gov]
Sent: Thursday, July 27, 2017 10:29 AM
To: Ex. 6 DOD (PP)
Ex. 6 DOD (PP) Wennerberg, Linda S. (HQ-LA000) (linda.s.wennerberg@nasa.gov) <linda.s.wennerberg@nasa.gov>; Moore, Beth <Beth.Moore@em.doe.gov>
Cc: Kim, Jim H. EOP/OMB < Ex. 6 Personal Privacy (PP) >; Dorjets, Vlad EOP/OMB < Ex. 6 Personal Privacy (PP)
Laity, Jim A. EOP/OMB < Ex. 6 Personal Privacy (PP)
Subject: Another High Quality Perchlorate Study

>http://www.nejm.org/doi/pdf/10.1056/NEJMoa1106104<

Antenatal Thyroid Screening and Childhood Cognitive Function

John H. Lazarus, M.D., Jonathan P. Bestwick, M.Sc., Sue Channon, D.Clin.Psych., Ruth Paradice, Ph.D., Aldo Maina, M.D., Rhian Rees, M.Sc., Elisabetta Chiusano, M.Psy., Rhys John, Ph.D., Varvara Guaraldo, M.S.Chem., Lynne M. George, H.N.C., Marco Perona, M.S.Chem., Daniela Dall'Amico, M.D., Arthur B. Parkes, Ph.D., Mohammed Joomun, M.Sc., and Nicholas J. Wald, F.R.S.

February 2012 NEJM

Another LARGE CONTROLLED study with hundreds of children finding that treatment of hypothyroidism did not result in improved cognitive function in

children at 3 years of age. What study quality criteria were applied in considering this study in comparison to UNCONTROLLED studies with small samples (e.g. Pop (1999) – 22 children and Pop (2003) – 57 children? Are these high quality studies that warrant quantitative analysis? Why?

What controls, if any, were applied in the five studies utilized by EPA (see EPA presentation slide 19)? What quality criteria applied – to assure that these are "quality" studies?

For comparison – see the new TSCA Framework Rulemaking just promulgated by EPA – some risk assessment guidelines to be followed by the TSCA office::

Below are some excerpts from the July 2017 risk evaluation rule referring to the weight of scientific evidence requirement. Here is a link to the final rule: >https://www.gpo.gov/fdsys/pkg/FR-2017-07-20/pdf/2017-14337.pdf<

§ 702.33 Definitions.

Weight of scientific evidence means a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a preestablished protocol to **comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.**

§ 702.41 Evaluation requirements.

(a) Considerations - (4) EPA will document that it has used the best available science and weight of scientific evidence approaches in the risk evaluation process.

(d) Hazard assessment –(2) The hazard assessment process will identify the types of hazards to health or the environment posed by the chemical substance under the condition(s) of use within the scope of the risk evaluation. **Hazard information related to potential health and environmental hazards of the chemical substance will be reviewed in a manner consistent with best available science and weight of scientific evidence as defined in § 702.33 and all assessment methods will be documented. This process includes the identification, evaluation, and synthesis of information to describe the potential health and environment hazards of the chemical substance.**
(e) Exposure assessment- (3) Exposure information related to potential human health or ecological hazards of the chemical substance will be reviewed in a manner consistent with the description of best available science and weight of scientific evidence in § 702.33 and all methods will be documented.

Did EPA comply with these fundamental scientific standards?

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/28/2017 4:37:47 PM
To: Grevatt, Peter [Grevatt.Peter@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Ex. 6 DOD (PP) Robert.Seifert@EM.Doe.Gov; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Margo_Schwab Ex. 6 Personal Privacy EOP (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy EOP (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick [Suzanne.Fitzpatrick@fda.hhs.gov]; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) kevin.bromberg@sba.gov; Ex. 6 DOD (PP) Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP) Mary.B.Neumayr Ex. 6 Personal Privacy EOP (PP) Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP) James_H_Kim Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy EOP (PP)

Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA
Location: EPA Headquarters East Bldg, 1201 Constitution Avenue NW, Room 2123

Start: 8/9/2017 7:00:00 PM
End: 8/9/2017 9:00:00 PM
Show Time As: Tentative

EPA headquarters "East" building, entrance on Constitution Avenue between 12th & 13th at Federal Triangle, https://www.epa.gov/aboutepa/visiting-epa-headquarters

Will follow up with additional visitor instructions as needed. Conference room 2123 in the East building.

Teleconference Ex. 6 Personal Privacy (PP) access code Ex. 6 Personal Privacy (PP)

Message

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/28/2017 3:28:30 PM
To: Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy (PP)]
CC: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: RE: Meeting w/ OMB on Perchlorate

Will do. I'm putting together an invite for Aug. 9, 3-5 p.m. at EPA.

-----Original Message-----
From: Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy (PP)]
Sent: Thursday, July 27, 2017 5:12 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Re: Meeting w/ OMB on Perchlorate

Please include Jim Laity too. Not sure if he was on last one.

Sent from my iPhone

> On Jul 27, 2017, at 5:08 PM, Dorjets, Vlad EOP/OMB <[Ex. 6 Personal Privacy (PP)]> wrote:
>
> Thanks for setting this up. I think it's fine for EPA to host this for a number of reasons. Monday at 11:00 and Wednesday at 3:00 both work on our end. Please feel free to send me an invitation for either one.
>
> I have copied all of the people from the last briefing below. Note that I did not try to remove EPA people.
>
> Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>;
> [Ex. 6 DOD (PP)]
> [Ex. 6 DOD (PP)]; Hafez, Ahmed
> <Hafez.Ahmed@epa.gov>; Robert.Seifert@EM.Doe.Gov; Strong, Jamie
> <Strong.Jamie@epa.gov>; Letitia.O'Conor@em.doe.gov; Mclain, Jennifer
> <Mclain.Jennifer@epa.gov>; Adamo, Emily (INTERN
> <Emily.Adamo@em.doe.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>;
> linda.s.wennerberg@nasa.gov; Burneson, Eric <Burneson.Eric@epa.gov>;
> tayyaba.waqar@sba.gov; Olson, Daniel <Olson.Daniel@epa.gov>;
> [Ex. 6 DOD (PP)]; Christ, Lisa <Christ.Lisa@epa.gov>;
> [Ex. 6 DOD (PP)] Schwab, Margo EOP/OMB
> <[Ex. 6 Personal Privacy (PP)]; Gareth.Buckland@em.doe.gov; White, Kamela
> G. EOP/OMB [Ex. 6 Personal Privacy (PP)]; Jensen, Sarah
> <Sarah.Jensen@Hq.Doe.Gov>; Barringer, Jody M. EOP/OMB
> [Ex. 6 Personal Privacy (PP)] Michael.Dinovi@fda.hhs.gov; Falk
> Curtin, Edna T. EOP/OMB <[Ex. 6 Personal Privacy (PP)]>;
> Annie.Lumen@fda.hhs.gov; Suzanne.Fitzpatrick@fda.hhs.gov; Abt, Eileen
> <Eileen.Abt@fda.hhs.gov>; Kluever, April <April.Kluever@fda.hhs.gov>;
> Jeffrey.Fisher@fda.hhs.gov; Clark, Steve <Steve.Clark@hq.doe.gov>;
> Moore, Beth <Beth.Moore@em.doe.gov>; [Ex. 6 DOD (PP)]
> [Ex. 6 DOD (PP)]
> Grossman, Andrea L. EOP/OMB <[Ex. 6 Personal Privacy (PP)]>;
> kevin.bromberg@sba.gov; [Ex. 6 DOD (PP)] Gamache, Christopher
> D. EOP/OMB <[Ex. 6 Personal Privacy (PP)]>; Neumayr, Mary B.
> EOP/CEQ <[Ex. 6 Personal Privacy (PP)]>; Lee, Jennifer M. EOP/OSTP
> <[Ex. 6 Personal Privacy (PP)]>; Kim, Jim H. EOP/OMB
> <[Ex. 6 Personal Privacy (PP)]>; [Ex. 6 DOD (PP)]; Behl, Betsy
> <Behl.Betsy@epa.gov>; OP ADP Calendar <OP_ADP_Calendar@epa.gov>;
> Nurse, Leanne <Nurse.Leanne@epa.gov>; Johnson, Ann
> <Johnson.Ann@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>;
> Schlosser, Paul <Schlosser.Paul@epa.gov>; Huff, Lisa
> <Huff.Lisa@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; Morozov,
> Viktor <Morozov.Viktor@epa.gov>; Bussard, David
> <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Seale,
> Viktoria Z. EOP/CEQ <[Ex. 6 Personal Privacy (PP)]>; Bahadori, Tina
> <Bahadori.Tina@epa.gov>; [Ex. 6 DOD (PP)]
> [Ex. 6 DOD (PP)]; Miller, Gregory
> <Miller.Gregory@epa.gov>; Wirtz, Mark S <Mark.Wirtz@fda.hhs.gov>;
> Gavelek, Alexandra <Alexandra.Gavelek@fda.hhs.gov>; Buckland, Gareth
> <Gareth.Buckland@NNSA.DOE.Gov>
>
>
> -----Original Message-----

> From: Muellerleile, Caryn [mailto:Muellerleile.Caryn@epa.gov]
> Sent: Thursday, July 27, 2017 4:26 PM
> To: Dorjets, Vlad EOP/OMB <Ex. 6 Personal Privacy (PP)
> Cc: Burneson, Eric <Burneson.Eric@epa.gov>
> Subject: RE: Meeting w/ OMB on Perchlorate
>
> Vlad, we have a few of the following dates/times as possibilities. Please let me know if any of these is preferable for you:
>
> Monday 8/7 - first choice 1:00-2:30, second choice 11:00-12:30 Wed.
> 8/9 - 3:00-4:30 Fri. 8/11 - 1:00-3:00
>
>
> Caryn Muellerleile
> Regulatory Management Division
> Office of Policy
> US Environmental Protection Agency
> 1200 Pennsylvania Ave NW (1803A)
> Washington, DC 20460
> (202) 564-2855
> muellerleile.caryn@epa.gov
>
>
>
> -----Original Message-----
> From: Burneson, Eric
> Sent: Thursday, July 27, 2017 3:46 PM
> To: Dorjets, Vlad EOP/OMB <Ex. 6 Personal Privacy (PP)
> Cc: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
> Subject: RE: Meeting w/ OMB on Perchlorate
>
> Thanks for setting this up Vlad. We will get names into the system by Tuesday and prepare for a good discussion on Thursday.
> Also please note that I have asked Caryn to work with you on scheduling the Federal Agencies meeting here during the week of August 7. Please note that I assumed it would be easier to host the meeting here at EPA where we have several large conference rooms but if you would prefer to hold it at the NEOB we are perfectly willing to come there.
> Eric
>
> -----Original Message-----
> From: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP)
> Sent: Thursday, July 27, 2017 3:16 PM
> To: Burneson, Eric <Burneson.Eric@epa.gov>
> Subject: Meeting w/ OMB on Perchlorate
>
> Eric,
>
> We're all set to meet over here next Thursday, August 3rd, at 4:00 to discuss perchlorate. The meeting will take place in our new offices on the 9th floor of NEOB (Conference Room 9258). Please enter the names of whomever you think may attend in the link below by COB Tuesday.
>
> Ex. 6 Personal Privacy (PP)
>
> I have attached our comments/questions to help inform your agenda and our discussion in general. Note that these comments are very similar to the ones we sent you after our initial phone call. We understand that you have already answered/addressed some of these questions but we thought it might be helpful to go over them one more time so that we can be clear of your response.
>
> Please don't hesitate to let me know if you have any questions about the attached list.
>
> Vlad
>
>

Message

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 8/8/2017 8:08:07 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Johnson, Ann [Johnson.Ann@epa.gov]; Schuck, Tracey [Schuck.Tracey@epa.gov]; Bradford, Charlotte [Bradford.Charlotte@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Attendee list for Aug. 9, 3-5 meeting:

Peter Grevatt, EPA
Jennifer McLain, EPA
Lynn Flowers, EPA
David Bussard, EPA
Ann Johnson, EPA
Ex. 6 DOD (PP)
Robert Seifert, DOE
Lisa August, OMB
Linda Wennerberg, NASA
Jody Barringer, OMB
Michael Dinovi, FDA
Eileen Abt, FDA
Annie Lumen, FDA
April Kluever, FDA
Beth Moore, DOE
Kevin Bromberg, SBA
Jim Kim, OMB
Viktoria Seale, CEQ
Jim Laity, OMB
Vlad Dorjets, OMB
Shruti Dabadi, EPA
Leanne Nurse, EPA
Betsy Behl, EPA
Ahmed Hafez, EPA

Tentative – Ex. 6 DOD (PP), Mark Wirtz/FDA, Mark Corrales/EPA

From: Burneson, Eric
Sent: Tuesday, August 08, 2017 3:37 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>; Schuck, Tracey <Schuck.Tracey@epa.gov>; Bradford, Charlotte <Bradford.Charlotte@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Caryn:

Thanks for your continued assistance organizing this meeting. I understand you will not be joining us tomorrow morning.

I do plan to ask you to distribute the following meeting materials by the end of the day today.

- A revised peer review charge
- A briefing document
- A table summary of the identified studies

I am hopeful we will have those materials soon but I doubt they will be ready by 4:30. Is there a way for you to check your email remotely later today and send it out? Alternatively I can send a note out to participants later.

Regarding access to the building, I have asked Tracey Schuck and Charlotte Bradford to be at the EPA East entrance starting at 2:30 to escort people into the building and to the 2123 conference room until a little after 3:00. . Can you provide an updated list of the individuals who accepted the invitation? And is there any indication of whether they are coming in person or not? We would want to get a list to security in advance.

From: Muellerleile, Caryn
Sent: Tuesday, August 08, 2017 3:06 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>
Subject: FW: Interagency briefing on Perchlorate Peer Review hosted by EPA

Hello Eric,

I think I will have to miss out on tomorrow morning's logistics call (I need to take leave from 8-12). Also, today I was planning to work until 4:30 but I am happy to check in later if there is something I should plan on sending out to tomorrow's attendees.

Is there an OW point of contact (name/tel) that I can provide to people in the event that there are any issues at the guards' desk tomorrow?

Thanks,
Caryn

From: Kluever, April [mailto:April.Kluever@fda.hhs.gov]
Sent: Tuesday, August 08, 2017 3:02 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Hi Caryn,

I'm planning on attending this meeting in person, coming down from the FDA CFSAN campus on the green line. Are there any special instructions for people coming in person? After going through security will I be able to go up to the conference room, or will I need an escort? Thanks so much,

April Kluever

April Neal Kluever, Ph.D., D.A.B.T.
Toxicologist

Center for Food Safety and Applied Nutrition (CFSAN)
Office of Food Additive Safety (OFAS)
Division of Food Contact Notifications (DFCN)
U.S. Food and Drug Administration
5001 Campus Drive, HFS 275
College Park, MD 20740
Tel: 240-402-1225
April.kluever@fda.hhs.gov

From: Muellerleile, Caryn [mailto:Muellerleile.Caryn@epa.gov]
Sent: Friday, August 04, 2017 10:12 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Vlad Dorjets ([redacted] Ex. 6 Personal Privacy (PP)
<[redacted] Ex. 6 Personal Privacy (PP)>; Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA

Thank you for your input on our charge for the peer review of methodologies to inform a perchlorate MCLG. We have continued to work on our characterization of the analysis and to improve the charge questions for the peer reviewers. We have planned an additional discussion with you for Wednesday August 9, to share more information and answer your questions about the draft analysis.

Please respond to me, Eric Burneson and Vlad Dorjets with the key issues or questions you would like us to address in the meeting on Wednesday so that we can be better prepared to discuss those concerns. We continue to consider the thoughtful input you have provided on the charge to this point and are preparing a revised charge for your consideration and comment. We will distribute the revised charge prior to the meeting.

Caryn Muellerleile
Regulatory Management Division
Office of Policy
US Environmental Protection Agency
1200 Pennsylvania Ave NW (1803A)
Washington, DC 20460
(202) 564-2855
muellerleile.caryn@epa.gov

Message

From: Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy (PP)]
Sent: 4/29/2019 8:46:15 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Nickerson, William [Nickerson.William@epa.gov]
Subject: RE: Missing Citation in Perchlorate NPRM

Thanks.

-----Original Message-----
From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, April 29, 2019 4:35 PM
To: Dorjets, Vlad EOP/OMB <[Ex. 6 Personal Privacy (PP)]
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM

Vlad:
Attached are the articles requested. Let me know if you need more 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

-----Original Message-----
From: Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy (PP)]
Sent: Monday, April 29, 2019 11:18 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM

Eric - See request below for three academic studies on IQ referenced in the NPRM. Could you please send me the papers when you can? Thanks.

-----Original Message-----
From: [Ex. 6 DOD (PP)]
Sent: Monday, April 29, 2019 9:55 AM
To: Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy (PP)]
Cc: Schwab, Margo EOP/OMB <[Ex. 6 Personal Privacy (PP)] [Ex. 6 DOD (PP)]
[Ex. 6 DOD (PP)]
Subject: Missing Citation in Perchlorate NPRM

In Section 10 where EPA describes meaningful IQ differences there are 3 citations missing. At this late point instead of just asking for the citations we are requesting EPA send us electronic copies of the papers, hopefully this is possible.
Would you please ask them to forward the following?
Bellinger (2004)
Rogan and Ware (2003)
Nation and Gleaves (2001)

Message

From: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP)
Sent: 4/26/2019 8:56:39 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: Re: Interagency Briefing on EPA's Proposed Perchlorate MCL

Thanks for clarifying

Sent from my iPhone

On Apr 26, 2019, at 3:01 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

> Vlad: The documentation of the responses to the 2017 peer review (and the 2018 peer review) are contained within the revised version of the MCLG Approaches Document I sent to you last week. Throughout that document we describe how we have modified our analyses in response to peer review recommendations. Let me know if there is something else you think that Tricia is looking for.
>
> 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: Dorjets, Vlad EOP/OMB < Ex. 6 Personal Privacy (PP)
Sent: Friday, April 26, 2019 11:04 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Fwd: Interagency Briefing on EPA's Proposed Perchlorate MCL

See below.

Sent from my iPhone

Begin forwarded message:

> **From:** Ex. 6 DOD (PP)
> Ex. 6 DOD (PP)
> **Date:** April 26, 2019 at 7:15:40 AM CDT
> **To:** "Dorjets, Vlad EOP/OMB" < Ex. 6 Personal Privacy (PP)
> **Cc:** Ex. 6 DOD (PP)
> **Subject: Re: Interagency Briefing on EPA's Proposed Perchlorate MCL**
>
> Vlad,
> Nice meeting and briefing from EPA. It's one of the better that I have seen.
>
> We have a question, did EPA document their responses to the 2017 peer review of the BBDR model and if so where can we find a copy?
>
> Thanks
> Ex. 6 DOD (PP)

Sent from my iPhone

On Apr 22, 2019, at 1:01 PM, Dorjets, Vlad EOP/OMB
<Ex. 6 Personal Privacy (PP) wrote:

The purpose of this briefing is for EPA to brief interagency reviewers on their draft proposal to set an MCLG and MCL for perchlorate, currently under EO 12866 review. Reviewers will also be able to ask questions about what EPA is seeking to do and why in order to inform their comments to OMB (due Monday, April 29th). The slides for the briefing are attached.

<Perchlorate Interagency Brief 4-25-19.pptx>

<meeting.ics>

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 4/29/2019 4:12:46 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]
Subject: FW: Missing Citation in Perchlorate NPRM
Attachments: Bellinger_2004_What is an adverse effect.pdf; Rogan_2003_Exposure to lead in children how low is enough.pdf; Nation_2001_ low level lead exposure and intelligence in children.pdf

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Monday, April 29, 2019 12:05 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Missing Citation in Perchlorate NPRM

Hi Lisa,

Here are the requested Papers.

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: Christ, Lisa
Sent: Monday, April 29, 2019 11:45 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM
Importance: High

Hi Sam,
Please provide the papers requested below. Hopefully they can be easily accessed?
Thanks,
Lisa

-----Original Message-----
From: Dorjets, Vlad EOP/OMB < Ex. 6 Personal Privacy (PP)
Sent: Monday, April 29, 2019 11:18 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM

Eric - See request below for three academic studies on IQ referenced in the NPRM. Could you please send me the papers when you can? Thanks.

-----Original Message-----
From: Ex. 6 DOD (PP)
Sent: Monday, April 29, 2019 9:55 AM
To: Dorjets, Vlad EOP/OMB
Cc: Schwab, Margo EOP/OMB Ex. 6 Personal Privacy (PP) Ex. 6 DOD (PP)
Ex. 6 DOD (PP)
Subject: Missing Citation in Perchlorate NPRM

In Section 10 where EPA describes meaningful IQ differences there are 3 citations missing. At this late point instead of just asking for the citations we are requesting EPA send us electronic copies of the papers, hopefully this is possible.
Would you please ask them to forward the following?
Bellinger (2004)

Rogan and Ware (2003)
Nation and Gleaves (2001)

Appointment

From: Kim, Jim H. EOP/OMB [redacted]
Sent: 7/9/2018 3:06:28 PM
To: [redacted] Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Waqar, Tayyaba [tayyaba.waqar@sba.gov]; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP [redacted]; Schwab, Margo EOP/OMB [redacted]; Laity, Jim A. EOP/OMB [redacted]; Szabo, Aaron L. EOP/CEQ [redacted]; Barringer, Jody M. EOP/OMB [redacted] Falk Curtin, Edna T. EOP/OMB [redacted]; Gamache, Christopher D. EOP/OMB [redacted]; Dorjets, Vlad EOP/OMB [redacted] Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fine, Leah R. EOP/OMB [redacted]

Subject: TWG - Perchlorate
Location: Conference Call

Start: 7/11/2018 6:00:00 PM
End: 7/11/2018 7:00:00 PM
Show Time As: Tentative

Recurrence: (none)

Dear Technical Working Group:

I am scheduling this conference call so that EPA can update us on their actions on regulating perchlorate in water. The external peer review of the scientific documents was completed last fall, and we have not had a recent update on the status of this activity.

Call-in Number: [redacted]
Participants: [redacted]

Let me know if you have questions.

Jim

Message

From: Grevatt, Peter [Grevatt.Peter@epa.gov]
Sent: 7/9/2018 2:01:39 PM
To: James_H_Kim [Ex. 6 Personal Privacy EOP (PP)]
CC: Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Burneson, Eric [Burneson.Eric@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Nickerson, William [Nickerson.William@epa.gov]
Subject: RE: Technical Working Group - EPA - perchlorate

Agreed. Jennifer i[Ex. 6 Personal Privacy (PP)]n this week, but Eric is in the office. I will be headed to Minneapolis tomorrow, but depending on the timing of the discussion, I may be able to participate as well.

From: Kim, Jim H. EOP/OMB [mailto:[Ex. 6 Personal Privacy EOP (PP)]
Sent: Monday, July 09, 2018 9:59 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Cc: Dorjets, Vlad EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]>; Burneson, Eric <Burneson.Eric@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Technical Working Group - EPA - perchlorate

Hi Peter,

Given the deadline of this October, I think it'd be good to get this meeting held this week. Is it ok if we proceed as long as Eric or Jennifer can make it?

Thanks,
Jim

From: Grevatt, Peter <Grevatt.Peter@epa.gov>
Sent: Sunday, July 8, 2018 5:36 PM
To: Kim, Jim H. EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]>
Cc: [Ex. 6 DOD (PP)]; Wennerberg, Linda S. (HQ-LD020) <linda.s.wennerberg@nasa.gov>; Seifert, Robert <Robert.Seifert@EM.Doe.Gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Waqar, Tayyaba <tayyaba.waqar@sba.gov>; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP <[Ex. 6 Personal Privacy EOP (PP)]>; Schwab, Margo EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]>; Laity, Jim A. EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]>; Szabo, Aaron L. EOP/CEQ <[Ex. 6 Personal Privacy EOP (PP)]>; Barringer, Jody M. EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]; Falk Curtin, Edna T. EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]>; Dorjets, Vlad EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]>; Tiago, Joseph <Tiago.Joseph@epa.gov>
Subject: Re: Technical Working Group - EPA - perchlorate

Thanks Jim. I'll be back in the office tomorrow, but then head back out for work travel Tues-Thursday. I'll be happy to participate when we are able to get this on folks calendars.

Sent from my iPhone

On Jul 3, 2018, at 12:23 PM, Kim, Jim H. EOP/OMB <[Ex. 6 Personal Privacy EOP (PP)]> wrote:

> Dear Technical Working Group:
>
> Some of you (Eric and Peter), have not yet been engaged in this interagency workgroup. But I think that you are aware of its purpose.

I would like to schedule a conference call either on Friday or early next week (Mon-Wed) to get a briefing from EPA on the current status of the perchlorate MCLG. Can you let me know your availability either by Doodle (link below) or by email?

>https://doodle.com/poll/zy2zrynqszsibncn<

Thanks,
Jim

James Kim, Ph.D., DABT
Office of Information and Regulatory Affairs
Office of Management and Budget

Ex. 6 Personal Privacy EOP (PP)

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 10/31/2017 9:33:46 PM
To: Gamache, Christopher D. EOP/OMB Ex. 6 Personal Privacy (PP)
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Thanks Chris and apologies.
Eric

From: Gamache, Christopher D. EOP/OMB Ex. 6 Personal Privacy (PP)
Sent: Tuesday, October 31, 2017 5:32 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric,

You may have included me by mistake, which means someone was left off the distribution list.
Just alerting you.

Thanks.

Chris Gamache
Program Examiner
OMB, Environment Branch
Ex. 6 Personal Privacy (PP)

From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Tuesday, October 31, 2017 5:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Gamache, Christopher D. EOP/OMB <Ex. 6 Personal Privacy (PP)
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I have a call into Ex. 6 DOD (PP) and would propose a conference call. Would that work for you ?

P.S. I don't think they want us to run the model for them just ask questions about how to run the model.

From: Morozov, Viktor
Sent: Tuesday, October 31, 2017 5:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Hi Eric,
What would be the best way to handle this? A conference call t Ex. 6 DOD (PP) ? Please see email for Paul.
-Viktor.

Viktor Morozov, Ph.D.
Chief, Quantitative Risk Methods Group (QRMG)
National Center for Environmental Assessment (NCEA), Washington Division (MC-8623P)
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Dr., Rm 11761
Arlington, Virginia 22202
Office: 703-347-8156
Ex. 6 Personal Privacy (PP)

From: Schlosser, Paul
Sent: Tuesday, October 31, 2017 4:46 PM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Also copying Dustin:

Depending on what exactly DOD wants, it shouldn't be hard to run some additional simulations with the perchlorate model.

Tomorrow morning I have a Ex. 6 Personal Privacy (PP), and then the talk that Dustin and I are doing for R5/States meeting in the afternoon, so it will be a little busy, but middle of the day is now clear.

-Paul

From: Bussard, David
Sent: Tuesday, October 31, 2017 4:21 PM
To: Morozov, Viktor <Morozov.Viktor@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: FW: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

I'm passing this on. I don't see attached questions, however.
David

From: Flowers, Lynn
Sent: Tuesday, October 31, 2017 4:11 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Hauchman, Fred <hauchman.fred@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Re: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

Eric: I am just about to check out! Interesting request. I suggest that you work with David Bussard to set up a call.
Lynn

Sent from my iPhone

On Oct 31, 2017, at 4:05 PM, Burneson, Eric <Burneson.Eric@epa.gov> wrote:

> Lynn and Fred: Please see the request we just received for assistance answering questions about the BBDR model from DOD. I would like to discuss with you our potential responses to this question. Lynn I recall you are either going out of town or will soon be departing which is why I

am including Fred.

I think a call would be appropriate. Who do you recommend be included in the discussion?

Eric

-----Original Message-----
From: Ex. 6 DOD (PP) [Ex. 6 Personal Privacy (PP)]
Sent: Tuesday, October 31, 2017 2:55 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: EPA Perchlorate Peer Review Comment Deadlines (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

Eric,
While reviewing the report, a question has emerged from our DoD toxicologists. We were wondering if we have a question about the model that could only be answered by someone running a model simulation, could we ask Paul Schlosser to do that? We are trying to get the model running here and answer any questions we have ourselves. However, one of our modelers just left to work for industry so we are a little short-handed right now and we are looking at all options.

Thank you for any help or thoughts on how to address this.

Ex. 6 DOD (PP)

-----Original Message-----
From: Burneson, Eric [mailto:Burneson.Eric@epa.gov]
Sent: Friday, October 6, 2017 4:03 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Ex. 6 Personal Privacy (PP) <Ex. 6 Personal Privacy (PP)>; Robert.Seifert@EM.Doe.Gov; August, Lisa L. EOP/OMB <Ex. 6 Personal Privacy (PP)>; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 Personal Privacy (PP)

Ex. 6 DOD (PP)

Margo_Schwab@Ex. 6 Personal Privacy (PP); Gareth.Buckland@em.doe.gov;

Kamela_G._White@[redacted]; Sarah.Jensen@Hq.Doe.Gov;
Jody_M._Barringer@[redacted]; Michael.Dinovi@fda.hhs.gov;
Edna_F._Curtin@[redacted]; Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick
<Suzanne.Fitzpatrick@fda.hhs.gov>; Eileen.Abt@fda.hhs.gov; Apri
l.Kluever@fda.hhs.gov; Jeff Fisher <Jeffrey.Fisher@fda.hhs.gov>; Steve.Clark@hq.doe.gov;
Beth.Moore@em.doe.gov; [redacted]
[redacted]>; Andrea_L_Grossman@[redacted]; kevin.bromberg@sba.gov;
[redacted]
Christopher_D_Gamache@[redacted]; Mary.B.Neumayr@[redacted];
Jennifer_M_Lee@[redacted]; James_H_Kim@[redacted]
Viktoria.Z.Seale@[redacted]; [redacted]
<[redacted]>; Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov;
Gareth.Buckland@NNSA.DOE.Gov; James A. Laity <[redacted]>; Vlad
Dorjets ([redacted]>; Kabadi, Shruti
<Shruti.Kabadi@fda.hhs.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Chin, Teung
<Teung.Chin@ARS.USDA.GOV>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <St
rong.Jamie@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hafez, Ahmed
<Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Kunickis, Sheryl - OSEC
<Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
<[redacted]>; Corrales, Mark <Corrales.Mark@epa.gov>; Domesle,
Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; DCRoomEast2123/DC-ICC-OW-
OGWDW <DCRoomEast2123@epa.gov>; [redacted]
[redacted]>; Robert.Seifert@EM.Doe.Gov; August, Lisa L.
EOP/OMB <[redacted]>; Letitia.O'Conor@em.doe.gov;
Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; [redacted]
[redacted]
Margo_Schwab@[redacted]; Gareth.Buckland@em.doe.gov;
Kamela_G._White@[redacted]; Sarah.Jensen@Hq.Doe.Gov;
Jody_M._Barringer@[redacted]; Michael.Dinovi@fda.hhs.gov; Edna_F._Cu
rtin@[redacted]; Annie.Lumen@fda.hhs.gov; Eileen.Abt@fda.hhs.gov;
April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; [redacted]
[redacted]
Andrea_L_Grossman@[redacted]; [redacted]
[redacted]
Christopher_D_Gamache@[redacted]; Mary.B.Neumayr@[redacted]
Jennifer_M_Lee@[redacted]; Viktoria.Z.Seale@[redacted]; [redacted]
[redacted]; Mark.Wirtz@fda.hhs.gov;
Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity
<[redacted]>; Vlad Dorjets ([redacted]
<[redacted]>; Kabadi, Shruti <Shruti.Kabadi@fda.hhs.gov>; Chin, Teung
<Teung.Chin@ARS.USDA.GOV>; Kunickis, Sheryl - OSEC
<Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
<[redacted]
.gov>; Domesle, Alexander - ARS <Alexander.Domesle@ARS.USDA.GOV>; [redacted]
[redacted]; Robert.Seifert@EM.Doe.Gov;
August, Lisa L. EOP/OMB <[redacted]>; Letitia.O'Conor@em.doe.gov;
Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; [redacted]
[redacted]
[redacted]
Margo_Schwab@[redacted]; Gareth.Buckland@em.doe.gov;

Kamela_G._White@[redacted] Sarah.Jensen@Hq.Doe.Gov;
Jody_M._Barringer@[redacted] Michael.Dinovi@fda.hhs.gov;
Edna_F._Curtin@[redacted] Annie.Lumen@fda.hhs.gov; Eileen.Abt@fda.hhs.gov;
April.Kluever@fda.hhs.gov; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; [redacted]
[redacted]
[redacted] Andrea_L_Grossman@[redacted]
[redacted]; Christopher_D_Gamache@[redacted]
Mary.B.Neumayr@[redacted] Jennifer_M_Lee@[redacted]; [redacted]
Viktoria.Z.Seale@[redacted] [redacted]
[redacted] Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov;
Gareth.Buckland@NNSA.DOE.Gov; James A. Laity <[redacted]>; Vlad
Dorjets [redacted]; Kabadi, Shruti
<Shruti.Kabadi@fda.hhs.gov>; Chin, Teung <Teung.Chin@ARS.USDA.GOV>; Kunickis,
Sheryl - OSEC <Sheryl.Kunickis@osec.usda.gov>; Jensen, Michael C. EOP/CEQ
<[redacted]>; Domesle, Alexander - ARS
<Alexander.Domesle@ARS.USDA.GOV>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: [Non-DoD Source] EPA Perchlorate Peer Review Comment Deadlines

Federal Partners:

As we have discussed previously, EPA currently has two pending requests for comment related to the perchlorate peer review.

1. The deadline for comments on the charge question and potential peer reviewers is today. The comment deadline for this request remains unchanged. Note that you have the option of sending your comments directly to me via email.

2. The current deadline for the comments on the report is October 30, 2017. EPA will be extending the deadline for the comments on the Draft Report and Model by 21 days. We expect to publish a comment deadline extension (to Nov. 20) in the Federal Register next week.

Thank you for your continued input 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

CLASSIFICATION: UNCLASSIFIED

Appointment

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 8/9/2017 4:17:44 PM
CC: Schuck, Tracey [Schuck.Tracey@epa.gov]; Bradford, Charlotte [Bradford.Charlotte@epa.gov]

Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA
Location: EPA East Entrance

Start: 8/9/2017 6:30:00 PM
End: 8/9/2017 7:00:00 PM
Show Time As: Tentative

Tracey can you please go to the EPA East entrance and escort the non EPA individuals to the meeting in room 2123.

From: Muellerleile, Caryn
Sent: Tuesday, August 08, 2017 4:08 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>; Schuck, Tracey <Schuck.Tracey@epa.gov>; Bradford, Charlotte <Bradford.Charlotte@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Attendee list for Aug. 9, 3-5 meeting:

Peter Grevatt, EPA
Jennifer McLain, EPA
Lynn Flowers, EPA
David Bussard, EPA
Ann Johnson, EPA

Ex. 6 DOD (PP)

Robert Seifert, DOE
Lisa August, OMB
Linda Wennerberg, NASA
Jody Barringer, OMB
Michael Dinovi, FDA
Eileen Abt, FDA
Annie Lumen, FDA
April Kluever, FDA
Beth Moore, DOE
Kevin Bromberg, SBA
Jim Kim, OMB
Viktoria Seale, CEQ
Jim Laity, OMB
Vlad Dorjets, OMB
Shruti Dabadi, EPA
Leanne Nurse, EPA
Betsy Behl, EPA

Ahmed Hafez, EPA

Tentative – Ex. 6 DOD (PP), Mark Wirtz/FDA, Mark Corrales/EPA

From: Burneson, Eric
Sent: Tuesday, August 08, 2017 3:37 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>; Schuck, Tracey <Schuck.Tracey@epa.gov>; Bradford, Charlotte <Bradford.Charlotte@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Caryn:
Thanks for your continued assistance organizing this meeting. I understand you will not be joining us tomorrow morning.

I do plan to ask you to distribute the following meeting materials by the end of the day today.

- A revised peer review charge
- A briefing document
- A table summary of the identified studies

I am hopeful we will have those materials soon but I doubt they will be ready by 4:30. Is there a way for you to check your email remotely later today and send it out? Alternatively I can send a note out to participants later.

Regarding access to the building, I have asked Tracey Schuck and Charlotte Bradford to be at the EPA East entrance starting at 2:30 to escort people into the building and to the 2123 conference room until a little after 3:00. . Can you provide an updated list of the individuals who accepted the invitation? And is there any indication of whether they are coming in person or not? We would want to get a list to security in advance.

From: Muellerleile, Caryn
Sent: Tuesday, August 08, 2017 3:06 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>
Subject: FW: Interagency briefing on Perchlorate Peer Review hosted by EPA

Hello Eric,

I think I will have to miss out on tomorrow morning's logistics call (I need to take leave from 8-12). Also, today I was planning to work until 4:30 but I am happy to check in later if there is something I should plan on sending out to tomorrow's attendees.

Is there an OW point of contact (name/tel) that I can provide to people in the event that there are any issues at the guards' desk tomorrow?

Thanks,
Caryn

From: Kluever, April [mailto:April.Kluever@fda.hhs.gov]
Sent: Tuesday, August 08, 2017 3:02 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Hi Caryn,

I'm planning on attending this meeting in person, coming down from the FDA CFSAN campus on the green line. Are there any special instructions for people coming in person? After going through security will I be able to go up to the conference room, or will I need an escort? Thanks so much,

April Kluever

April Neal Kluever, Ph.D., D.A.B.T.
Toxicologist

Center for Food Safety and Applied Nutrition (CFSAN)
Office of Food Additive Safety (OFAS)
Division of Food Contact Notifications (DFCN)
U.S. Food and Drug Administration
5001 Campus Drive, HFS 275
College Park, MD 20740
Tel: 240-402-1225
April.kluever@fda.hhs.gov

From: Muellerleile, Caryn [mailto:Muellerleile.Caryn@epa.gov]
Sent: Friday, August 04, 2017 10:12 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Vlad Dorjets Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA

Thank you for your input on our charge for the peer review of methodologies to inform a perchlorate MCLG. We have continued to work on our characterization of the analysis and to improve the charge questions for the peer reviewers. We have planned an additional discussion with you for Wednesday August 9, to share more information and answer your questions about the draft analysis.

Please respond to me, Eric Burneson and Vlad Dorjets with the key issues or questions you would like us to address in the meeting on Wednesday so that we can be better prepared to discuss those concerns. We continue to consider the thoughtful input you have provided on the charge to this point and are preparing a revised charge for your consideration and comment. We will distribute the revised charge prior to the meeting.

Caryn Muellerleile
Regulatory Management Division
Office of Policy
US Environmental Protection Agency

1200 Pennsylvania Ave NW (1803A)
Washington, DC 20460
(202) 564-2855
muellerleile.caryn@epa.gov

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/29/2019 8:34:41 PM
To: Vlad Dorjets [Ex. 6 Personal Privacy (PP)]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Nickerson, William [Nickerson.William@epa.gov]
Subject: FW: Missing Citation in Perchlorate NPRM
Attachments: Bellinger_2004_What is an adverse effect.pdf; Rogan_2003_Exposure to lead in children how low is enough.pdf; Nation_2001_ low level lead exposure and intelligence in children.pdf

Vlad:
Attached are the articles requested. Let me know if you need more 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

-----Original Message-----
From: Dorjets, Vlad EOP/OMB <[Ex. 6 Personal Privacy (PP)]>
Sent: Monday, April 29, 2019 11:18 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM

Eric - See request below for three academic studies on IQ referenced in the NPRM. Could you please send me the papers when you can? Thanks.

-----Original Message-----
From: [Ex. 6 DOD (PP)]
Sent: Monday, April 29, 2019 9:55 AM
To: Dorjets, Vlad EOP/OMB <[Ex. 6 Personal Privacy (PP)]>
Cc: Schwab, Margo EOP/OMB <[Ex. 6 Personal Privacy (PP)]>; [Ex. 6 DOD (PP)]
[Ex. 6 DOD (PP)]
Subject: Missing Citation in Perchlorate NPRM

In Section 10 where EPA describes meaningful IQ differences there are 3 citations missing. At this late point instead of just asking for the citations we are requesting EPA send us electronic copies of the papers, hopefully this is possible.
Would you please ask them to forward the following?
Bellinger (2004)
Rogan and Ware (2003)
Nation and Gleaves (2001)

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/26/2019 5:21:01 PM
To: Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]; Khera, Rajiv [Khera.Rajiv@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: FW: Interagency Briefing on EPA's Proposed Perchlorate MCL

Sam do we have the document requested below regarding peer review?

From: Dorjets, Vlad EOP/OMB <Ex. 6 Personal Privacy (PP)
Sent: Friday, April 26, 2019 11:04 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: Fwd: Interagency Briefing on EPA's Proposed Perchlorate MCL

See below.

Sent from my iPhone

Begin forwarded message:

> **From:** "Ex. 6 DOD (PP)
> **Date:** April 26, 2019 at 7:15:40 AM CDT
> **To:** "Dorjets, Vlad EOP/OMB" <Ex. 6 Personal Privacy (PP)
> **Cc:** "Ex. 6 DOD (PP)
> **Subject: Re: Interagency Briefing on EPA's Proposed Perchlorate MCL**
>
> Vlad,
> Nice meeting and briefing from EPA. It's one of the better that I have seen.
>
> We have a question, did EPA document their responses to the 2017 peer review of the BBDR model and if so where can we find a copy?
>
> Thanks
> Ex. 6 DOD (PP)
>
> Sent from my iPhone
>
>> On Apr 22, 2019, at 1:01 PM, Dorjets, Vlad EOP/OMB <Ex. 6 Personal Privacy (PP) wrote:
>>
>> The purpose of this briefing is for EPA to brief interagency reviewers on their draft proposal to set an MCLG and MCL for perchlorate, currently under EO 12866 review. Reviewers will also be able to ask questions about what EPA is seeking to do and why in order to inform their comments to OMB (due Monday, April 29th). The slides for the briefing are attached.
>>
>> <Perchlorate Interagency Brief 4-25-19.pptx>
>>
>> <meeting.ics>

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 4/29/2019 4:11:44 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Hernandez-Quinones, Samuel [hernandez.samuel@epa.gov]
Subject: FW: Missing Citation in Perchlorate NPRM

Can we get copies of these papers?

-----Original Message-----
From: Dorjets, Vlad EOP/OMB < Ex. 6 Personal Privacy (PP)
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Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM

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To: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP) />
Cc: Schwab, Margo EOP/OMB Ex. 6 DOD (PP)
Ex. 6 DOD (PP)
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Rogan and Ware (2003)
Nation and Gleaves (2001)

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From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/6/2017 6:02:35 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Ex. 6 Personal Privacy (PP)]; Vlad Dorjets [Ex. 6 Personal Privacy (PP)]
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim@[Ex. 6 Personal Privacy (PP)]; Barringer, Jody M. EOP/OMB [Ex. 6 Personal Privacy (PP)]; Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; [Ex. 6 DOD (PP)] [Ex. 6 DOD (PP)] Seale, Viktoria Z. EOP/CEQ [Ex. 6 Personal Privacy (PP)]; Bahadori, Tina [Bahadori.Tina@epa.gov]; [Ex. 6 DOD (PP)] Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN) [Emily.Adamo@em.doe.gov]; [Ex. 6 DOD (PP)] [Ex. 6 DOD (PP)] Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]

Subject: Canceled: Interagency Perchlorate Peer Review Briefing with EPA
Location: teleconference [Ex. 6 Personal Privacy (PP)] / access code [Ex. 6 Personal Privacy (PP)]

Start: 7/10/2017 2:00:00 PM
End: 7/10/2017 3:00:00 PM
Show Time As: Free

Importance: High

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 8/2/2017 8:14:45 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Behl, Betsy [Behl.Betsy@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Ex. 6 DOD (PP) Robert.Seifert@EM.Doe.Gov; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Margo_Schwab Ex. 6 Personal Privacy EOP (PP); Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy EOP (PP); Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick [Suzanne.Fitzpatrick@fda.hhs.gov]; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) kevin.bromberg@sba.gov; Ex. 6 DOD (PP) Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP) Mary.B.Neumayr Ex. 6 Personal Privacy EOP (PP) Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP) James_H_Kim Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity [James_A._Laity Ex. 6 Personal Privacy EOP (PP) Vlad Dorjets (Vladik_Dorjets Ex. 6 Personal Privacy EOP (PP) [Vladik_Dorjets Ex. 6 Personal Privacy EOP (PP)
CC: Kabadi, Shruti [Shruti.Kabadi@fda.hhs.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Chin, Teung [Teung.Chin@ARS.USDA.GOV]

Subject: FW: Interagency briefing on Perchlorate Peer Review hosted by EPA
Location: EPA Headquarters East Bldg, 1201 Constitution Avenue NW, Room 2123

Start: 8/9/2017 7:00:00 PM
End: 8/9/2017 9:00:00 PM
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-----Original Appointment-----
From: Muellerleile, Caryn
Sent: Friday, July 28, 2017 11:22 AM
To: Muellerleile, Caryn; Grevatt, Peter; Mclain, Jennifer; Burneson, Eric; Flowers, Lynn; Bussard, David; Johnson, Ann; Ex. 6 DOD (PP) Robert.Seifert@EM.Doe.Gov; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Margo_Schwab Ex. 6 Personal Privacy EOP (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy EOP (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP) Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 DOD (PP) Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) kevin.bromberg@sba.gov; Ex. 6 DOD (PP) Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP) Mary.B.Neumayr Ex. 6 Personal Privacy EOP (PP) Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP) James_H_Kim Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP); Ex. 6 DOD (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity; Vlad Dorjets (Vladik_Dorjets Ex. 6 Personal Privacy EOP (PP)
Cc: Kabadi, Shruti; OP ADP Calendar; Nurse, Leanne; Chin, Teung
Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA
When: Wednesday, August 09, 2017 3:00 PM-5:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: EPA Headquarters East Bldg, 1201 Constitution Avenue NW, Room 2123

EPA headquarters "East" building, entrance on Constitution Avenue between 12th & 13th at Federal Triangle, https://www.epa.gov/aboutepa/visiting-epa-headquarters

Will follow up with additional visitor instructions as needed. Conference room 2123 in the East building.

Teleconference Ex. 6 Personal Privacy (PP) access code Ex. 6 Personal Privacy (PP)

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/10/2017 6:00:52 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Margo_Schwab Ex. 6 Personal Privacy EOP (PP)]; Vlad Dorjets Ex. 6 Personal Privacy EOP (PP)
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim Ex. 6 Personal Privacy EOP (PP) ; Barringer, Jody M. EOP/OMB Ex. 6 Personal Privacy EOP (PP) ; Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Seale, Viktoria Z. EOP/CEQ Ex. 6 Personal Privacy EOP (PP) Bahadori, Tina [Bahadori.Tina@epa.gov]; Ex. 6 DOD (PP) Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN [Emily.Adamo@em.doe.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]; Buckland, Gareth [Gareth.Buckland@NNSA.DOE.Gov]; Clark, Steve [Steve.Clark@hq.doe.gov]; Neumayr, Mary B. EOP/CEQ Ex. 6 Personal Privacy EOP (PP)

Subject: Interagency Perchlorate Peer Review Briefing with EPA (rescheduled)
Location: teleconference Ex. 6 Personal Privacy (PP) / access code Ex. 6 Personal Privacy (PP)

Start: 7/18/2017 6:00:00 PM
End: 7/18/2017 7:00:00 PM
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Draft agenda:

Ex. 5 Deliberative Process (DP)

EPA's recent model and peer review materials:
https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0438
https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0439

Revised briefing materials to follow.

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/6/2017 6:02:35 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Ex. 6 Personal Privacy (PP)]; Vlad Dorjets [Ex. 6 Personal Privacy (PP)]
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Location: teleconference [Ex. 6 Personal Privacy (PP)] / access code [Ex. 6 Personal Privacy (PP)]

Start: 7/10/2017 2:00:00 PM
End: 7/10/2017 3:00:00 PM
Show Time As: Free

Importance: High

Margo & Vlad – please share with other interagency partners. Materials to follow.

United States
Environmental Protection
Agency

Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

Volume I

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Appendix D – Overview of Group 3 Studies

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Abbreviations and Acronyms

AACC	American Association for Clinical Chemistry
ADHD	Attention deficit/hyperactivity disorder
AITD	Autoimmune thyroid disorder
ANT	Amsterdam Neuropsychological Test
ASD	Autism spectrum disorder
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	Biologically based dose-response
BEI	Butanol-extractable iodine
BMI	Body mass index
BSID	Bayley Scales of Infant Development
BW	Body weight
CBCL	Child Behavior Checklist
CCL	Contaminant Candidate List
CTD	Comparative Toxicogenomics Database
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FiPS-S	Finnish Prenatal Study of Schizophrenia
FMC	Finnish Maternity Cohort
FSIQ	Full-scale IQ
fT3	Free triiodothyronine
fT4	Free thyroxine
GW	Gestational week(s)
GSD	Geometric Standard Deviation
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HPT	Hypothalamic-pituitary-thyroid
HRL	Health reference level
IQ	Intelligence quotient
IQR	Interquartile range
KI	Potassium iodine
LDL	Low-density lipoprotein
MCLG	Maximum contaminant level goal
MDI	Mental Development Index (of the BSID)
MOA	Mode of action
MS	Mass spectrometry
NHANES	National Health and Nutrition Examination Survey
NIS	Sodium-iodide symporter
NOAEL	No observed adverse effects level
NRC	National Research Council
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PBDE	Polybrominated diphenyl ether
PBPK-PD	Physiologically based pharmacokinetic/pharmacodynamic
PC	Partition coefficient
PCB	Polychlorinated biphenyl
PDI	Psychomotor Development Index (of the BSID)
PDP	Pervasive Developmental Problems Scale
PFA	Perfluorinated acid
PIQ	Performance IQ

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PND	Post-natal days
PPVT	Peabody Picture and Vocabulary Test
RfD	Reference dose
ROB	Rest-of-body
RR	Relative risk
RSC	Relative source contribution
SAB	Science Advisory Board
SD	Standard deviation
SDWA	Safe Drinking Water Act
SRS	Social Responsiveness Scale
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-binding globulin
TFT	Thyroid function test
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
THoP	Transient hypothyroxinemia of prematurity
TPO Ab	Thyroid peroxidase antibody
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone (or thyrotropin)
tT3	Total triiodothyronine
tT4	Total thyroxine
TTR	Transthyretin
VIQ	Verbal IQ
VRM	Visual Recognition Memory
WISC-III	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAVMA	Wide Range Assessment of Visual Motor Ability

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Executive Summary

EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate in accordance with recommendations made by the Agency's Science Advisory Board. EPA has developed and peer reviewed a biologically-based dose-response (BBDR; also known as a physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD)) model that predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages.

The purpose of this document is to present the revisions to the BBDR model in response to the prior peer review and to present alternative approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects. The document does not derive an MCLG; rather, it presents alternative approaches that might be used to inform future decisions including the derivation of an MCLG in accordance with the Safe Drinking Water Act (SDWA).

MCLGs are non-enforceable, health-based goals that EPA sets for each regulated drinking water contaminant. In accordance with the SDWA, they are set at a level at which no known or anticipated adverse human health effect occur 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.

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 PBPK/PD modeling;
- 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" (SAB, 2013, p. 19).

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

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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

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 Section 3 of this report; additional detail is available in Appendix A. 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.

EPA has developed a two-stage approach linking the revised BBDR model results ("stage 1") with quantitative information on neurodevelopmental outcomes from epidemiological studies ("stage 2"). 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.

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). EPA presents and characterizes all of these studies in Section 5 of this report.

Using the output from the revised BBDR model and the quantitative relationships between thyroid hormone levels and neurodevelopmental effects from the published epidemiological studies EPA characterized the relationship between perchlorate exposure on free T4 (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.

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1. Introduction

EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate. EPA has developed and peer reviewed a biologically-based dose-response (BBDR; also known as a PBPK/PD) model that predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages. This document presents revisions made to the BBDR model in response to the prior peer review and presents alternative approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects.

1.1 Background on Perchlorate

Perchlorate has both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas, particularly those with arid environments (Trumpolt et al., 2005). In the past, nitrate fertilizers from Chilean deposits that contained perchlorate were widely used in the United States, which resulted in perchlorate contamination of soil and plants (Agency for Toxic Substances and Disease Registry (ATSDR, 2008)). 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). Perchlorate is also generated during the manufacture and use of pyrotechnic devices such as fireworks (ATSDR, 2008). It is difficult to determine the annual production of perchlorate in these industries, as perchlorate is not included on EPA's Toxics Release Inventory list of chemicals that must be reported. In 1994, annual production of perchlorate was estimated to be approximately 22 million pounds (ATSDR, 2008).

1.1.1 Chemical Identity of Perchlorate

Perchlorate is a negatively charged ion that is comprised of one chlorine atom and four oxygen atoms and is released to the environment in the form of a salt (a type of ionic compound) (NRC, 2005). The most common perchlorate salt produced in the United States is ammonium perchlorate, with magnesium, potassium, sodium, and lithium perchlorate also generated in substantial amounts (ATSDR, 2008). Perchlorate is highly stable and mobile in the aqueous environment, since the perchlorate salts are very soluble in water and do not adsorb to soil or sediment (NRC, 2005). Because of their low vapor pressure, perchlorate salts do not volatilize into the air from water (ATSDR, 2008).

1.1.2 Overview of Human Exposure and Health Effects

Humans are primarily exposed to perchlorate from ingestion of contaminated food and drinking water supplies (NRC, 2005). EPA's analysis of nationally representative data from the first Unregulated Contaminant Monitoring Rule found that 4.1% of 3,865 public water systems tested for perchlorate had concentrations above method reporting limit (MRL) of 4 µg/L. (U.S. EPA, 2008). The average concentration of perchlorate in samples above the MRL was 9.85 µg/L, with a maximum concentration of 420 µg/L (U.S. EPA, 2008). In an analysis of foods from the U.S. Food and Drug Administration's (FDA's) Total Diet Study, approximately three-quarters of the foods tested had at least one sample with detectable levels of perchlorate (Murray, Egan, Kim, Beru, & Bolger, 2008). Dietary sources with detectable levels of perchlorate include, but are not limited to, cow's milk, breast milk, and lettuce (ATSDR, 2008; Kirk, Smith, Tian, Anderson, & Dasgupta, 2003; Sharp & Lunder, 2003). Ingestion exposures are of concern because perchlorate is easily and almost completely absorbed from the gastrointestinal tract (Srinivasan & Viraraghavan, 2009). In a 2004-

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2005 perchlorate dietary exposure study, FDA estimated the average dietary perchlorate exposure for all persons aged 2 and above was 0.053 µg/kg bw/day (FDA, 2015). In 2016, FDA estimated average perchlorate dietary intake for the total U.S. population increased from their previous assessment and ranged between 0.13 to 0.15 µg/kg bw/day, with estimated average intakes ranging between 0.09 and 0.48 µg/kg bw/day based on age (Abt, Spungen, Pouillot, Gamalo-Siebers, & Wirtz, 2016). Inhalation and dermal exposures to perchlorate in the general population are considered to be negligible due to perchlorate's low potential for volatilization and for absorption from the skin (NRC, 2005). However, occupational exposures to perchlorate via inhalation of perchlorate dust or deposition into the mouth may occur (ATSDR, 2008).

Blount et al. (2006) measured perchlorate in urine samples collected from a sample of U.S. residents as part of the 2001-2002 National Health and Nutrition Examination Survey (NHANES). Blount et al., (2006) detected perchlorate at concentrations greater than 0.05 µg/L in all urine samples tested, with a median concentration of 3.6 µg/L (95th percentile at 14 µg/L). Women of reproductive age (15-44 years) had a median urinary perchlorate concentration of 2.9 µg/L (95th percentile at 13 µg/L). The demographic with the highest concentration of urinary perchlorate was children (6-11 years), who had a median urinary perchlorate concentration of 5.2 µg/L. Blount et al. (2006) estimated a total daily perchlorate dose for the NHANES participants aged 20 and older and found a median dose of 0.066 µg/kg/day and estimated a 95th percentile dose of 0.234 µg/kg/day. In a study analyzing perchlorate exposure trends using NHANES cohorts from 2005-2014 it was found that urinary perchlorate concentrations ranged from 2.63 ng/mL to 3.86 ng/mL, with urinary perchlorate decreasing over this time period (Corey, Bell, & Pleus, 2017).

The main target organ for perchlorate's toxicity is the thyroid gland (ATSDR, 2008). Specifically, perchlorate competes with iodide for transport through the sodium-iodide symporter (NIS) into the thyroid gland, which is a necessary step in the production of thyroid hormones T3 and T4(NRC, 2005). Therefore, perchlorate may lead to decreases in levels of these hormones (ATSDR, 2008; Blount, Pirkle, Osterloh, Valentin-Blasini, & Caldwell, 2006; NRC, 2005; Steinmaus, Miller, Cushing, Blount, & Smith, 2013; Steinmaus et al., 2016) by decreasing iodide uptake. Thyroid hormones are essential to the growth and development of fetuses, infants, and young children, as well as to metabolism and energy regulation throughout the lifespan (NRC, 2005). Disturbances in thyroid levels can adversely affect systems throughout the body, including the cardiovascular, pulmonary, and reproductive systems (ATSDR, 2008). Due to their critical role in the development and maintenance of body systems, thyroid hormones are well regulated in order to keep levels within a narrow range.

Reductions in thyroid hormone synthesis due to perchlorate exposures are also expected to lead to increases in thyroid-stimulating hormone or thyrotropin (TSH), a biomarker of thyroid hormone insufficiency as a result of diminished negative feedback (Mattie, Strawson, & Zhao, 2006). Several short-term (two-week exposure duration) studies have reported that exposures to higher doses of perchlorate in the general population were associated with decreases in iodide uptake, but not with changes in levels of thyroid hormones in the blood (Greer, Goodman, Pleus, & Greer, 2002; Lawrence, Lamm, & Braverman, 2001; Lawrence, Lamm, Pino, Richman, & Braverman, 2000). However, it must be noted that, because the adult euthyroid human thyroid contains several months of T4 stored in the colloid, it is not expected that a two-week study would result in a change in thyroid status.

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There is one small (n = 13), longer term clinical trial with six-months of perchlorate ingestion at rates of 0.5 or 3 mg of perchlorate ingestion per day that did not see any changes in thyroid function (Braverman et al., 2006). However, urinary iodide levels among participants in this study was considerably higher than the national average (mean 257.8 µg/total volume before 0.5 mg dose of perchlorate; mean 311.5 µg/total volume before 3 mg dose of perchlorate), which could be protective. This is consistent with evidence that healthy adults may be protected against the thyroid hormone changes associated with perchlorate exposures given adequate dietary iodine[1] intake (ATSDR, 2008).

Somewhat contradictory to these clinical exposure studies are several more recent epidemiological studies which have found associations between low levels of urinary perchlorate and TSH increases and T4 decreases (Blount et al., 2006; Steinmaus et al., 2013; Steinmaus et al., 2016). Specifically, Blount et al. (2006) found women with low urinary iodide to be particularly susceptible to altered thyroid hormone levels with perchlorate exposures. Additionally, Steinmaus et al. (2013) found an inverse relationship between thyroid hormone levels and perchlorate, and determined populations with concomitant exposures to other goitrogens (i.e., smokers) and low urinary iodide had an increased risk of altered thyroid hormone levels with perchlorate exposure. Furthermore, Steinmaus et al. (2016) evaluated a large pregnant population with early pregnancy exposure to perchlorate and found exposure to perchlorate to be associated with decreased fT4 and T4 and increased TSH.

Exposures to perchlorate and resulting changes in thyroid hormone levels may lead to adverse health effects, particularly in sensitive populations such as pregnant women, fetuses, and infants (Taylor et al., 2014). Thyroid hormones are critical to neurodevelopment of the fetus, and requirements for these hormones increase during pregnancy (Leung, Pearce, & Braverman, 2010). Taylor et al. (2014) found that mothers in the upper 10th percentile of perchlorate exposure during pregnancy had significantly increased odds of having offspring with intelligence quotient (IQ) scores in the lowest 10% of the population.

In addition, breastfed infants are completely dependent upon breast milk to provide iodine. Perchlorate exposures can lead to decreases in thyroid hormone levels in infants indirectly by decreasing iodine levels in breast milk or directly by decreasing hormone synthesis in infants, thereby leading to deficits in intellectual function (Leung et al., 2010). Individuals with thyroid conditions or iodine deficiencies are also expected to be at increased risk for adverse effects from perchlorate exposures (NRC, 2005).

1.2 Evaluation of Perchlorate under the Safe Drinking Water Act

EPA included perchlorate on the first three iterations of the Contaminant Candidate List (CCL), starting in 1998, after data collection and requests for comments. 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 EPA drinking water regulations. Contaminants listed on the CCL may require future regulation under SDWA. EPA uses the CCL to identify priority contaminants for regulatory decision making and information collection.

[1] For the purposes of this report, "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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In 2005, at the request of EPA and other federal agencies, the National Research Council (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). Significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of key thyroid hormones (T3 and T4), and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormone is potentially more likely to have adverse effects in sensitive populations (e.g., people with thyroid disorders, pregnant women, fetuses, and infants). Based on the NRC's recommendations, EPA adopted a 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 (7 μg/kg/day) identified by a study (Greer et al., 2002) in healthy adults for inhibition of radioactive iodide uptake and the application of an uncertainty factor of 10 for intraspecies variability.

In October 2008, EPA published a preliminary determination not to regulate perchlorate in drinking water using a health reference level (HRL) of 15 μg/L, which was derived from the RfD of 0.7 μg/kg/day, using a default body weight (70 kg), a default drinking water consumption rate (2 L/day), and a perchlorate-specific relative source contribution (RSC) of 62% for a pregnant woman (U.S. EPA, 2008). The RSC is the percentage of the RfD remaining for drinking water after the other sources of exposure to perchlorate (e.g., food) have been considered. In December 2008, 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 this issue. In August 2009, 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 body weight and exposure information (i.e., drinking water intake, RSC) (U.S. EPA, 2008). The HRLs ranged from 1 μg/L to 47 μg/L.

After considering comments on the October, 2008 and August, 2009 notices, EPA made a final determination to regulate perchlorate in drinking water in February 2011 (U.S. EPA, 2011). As a result of the determination, EPA initiated the process to develop an MCLG and National Primary Drinking Water Regulation for perchlorate under SDWA.

In accordance with SDWA, the Agency requested EPA's Science Advisory Board (SAB) to provide recommendations for how to consider available data in deriving a Maximum Contaminant Level Goal (MCLG) for use in developing a National Primary Drinking Water Regulation for perchlorate. EPA presented the SAB with a description of the general approach used by the Agency to derive an MCLG for non-carcinogenic chemicals. This approach relies on the following equation:

$$MCLG\ \left(\frac{\mu g}{L}\right) = \frac{RfD \times BW}{DWI} \times RSC$$

Where:

RfD = RfD of the contaminant (μg/kg/day); in the initial assessment for perchlorate, EPA used NRC's recommended RfD of 0.7 μg/kg/day

BW = body weight (kg)

DWI = drinking water ingestion rate (L/day)

RSC = relative source contribution

EPA also presented information to the SAB about life stage considerations, physiologically based pharmacokinetic modeling, epidemiologic and biomonitoring studies. 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 based upon its mode of action (MOA) rather than the default MCLG approach using the RfD and specific chemical exposure parameters" (SAB, 2013, p. 2). The SAB stated that this approach should follow perchlorate exposure through NIS inhibition to thyroid hormone change and finally to neurodevelopmental effects (SAB, 2013). This framework would incorporate the endpoint of iodide uptake inhibition that was the basis for the RfD as part of this broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes.

In addition, the SAB stated that EPA should more directly consider thyroid hormone changes as relevant to sensitive life stages; specifically, fetuses of hypothyroxinemic[2] pregnant women and infants and neonates exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women (SAB, 2013). This is because thyroid hormone deficiency is known to produce adverse effects on human neurodevelopment, an effect to which the above mentioned sensitive life stages are especially vulnerable. This direction is different from the conclusions of the NRC report, which based the RfD on the non-adverse effect of reduced iodide uptake and suggested examining pregnant women with hypothyroidism or iodide deficiency (NRC, 2005). The SAB approach focuses on the subtler changes in thyroid hormones (specifically fT4) associated with maternal hypothyroxinemia rather than broader changes in thyroid hormones (both fT4 and TSH) associated with hypothyroidism. Furthermore, the SAB recommended EPA consider available data on potential adverse health effects (i.e., neurodevelopmental outcomes) due to thyroid hormone level perturbations, regardless of the cause of those perturbations (SAB, 2013).

To address these recommendations, EPA revised the existing biologically based dose-response (BBDR) and PBPK-PD models (Lumen, Mattie, & Fisher, 2013; U.S. EPA, 2009) to create a 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 early gestation. EPA originally developed a set of 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, 2013)) with the pregnancy model representing the third trimester. These models were peer reviewed in January 2017[3]. Reviewers stressed the importance of developing an early pregnancy model when considering adverse neurodevelopmental impacts. This was confirmed by the results of EPA's literature review (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. Therefore, EPA responded to this peer review by developing an early pregnancy model

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[2] Free thyroxine (fT4) value at the lower end of the normal range with normal levels of TSH, as opposed to hypothyroidism, which consists of low levels of fT4 levels and high levels of TSH.

[3] For a more detailed discussion on the development of the draft model, its calibration, and dose-response evaluations, please see the 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 Analysis.* The report is available through the docket at http://www.regulations.gov *(Docket ID No. EPA-HQ-OW-2016-0439).*

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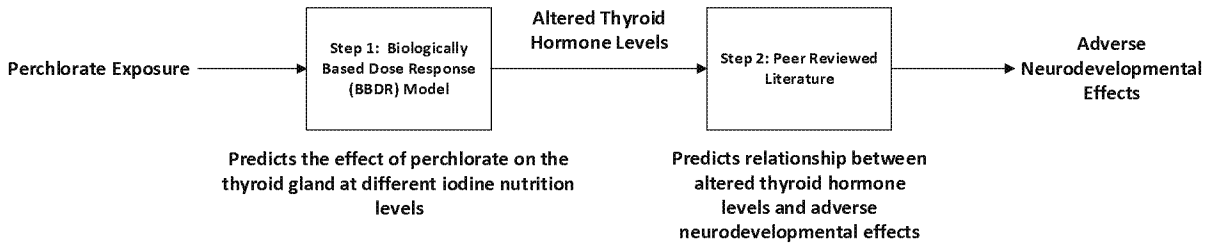
and updated key parameters for that model. The models for the other sensitive life stages were not revised given the importance of early pregnancy thyroid hormones on offspring neurodevelopment (de Escobar, Obregón, & del Rey, 2004; Korevaar et al., 2016; Pop et al., 2003; Pop et al., 1999). Consequently, this report concentrates on fetuses of hypothyroxinemic women early in pregnancy as the sensitive life stage.

1.3 Objective of the Report

The purpose of this document is to present revisions made to the BBDR model in response to the prior peer review and to present alternative approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects. The document does not derive an MCLG; rather, it presents alternative approaches that might be used to inform future decisions including the derivation of an MCLG in accordance with the SDWA (see Figure 1).

Figure 1. Summary of Modeling Approach for Estimating Measurable Adverse Neurodevelopmental Impacts from Perchlorate Exposure in Pregnant Woman



Section 2 of the report describes how perchlorate can disrupt thyroid hormone homeostasis along with the common causes and consequences of such disruptions, including neurodevelopmental alterations following the proposed MOA put forward by the NRC and modified by the SAB. Section 3 of the report provides overview of EPA's BBDR model and Section 4 of the report provides a description of how the output of the BBDR model relates to a distribution of thyroid hormone levels. The remainder of the report is focused on connecting the predicted changes in thyroid hormone levels from the BBDR model to downstream impacts, indicated as Step 2 in Figure 1. Section 5 provides details on the literature search and review process that led to the identification of studies to link the BBDR model outputs to quantitative alterations in neurodevelopmental endpoints. Section 6 outlines an approach to utilize the identified studies to link the revised perchlorate BBDR model predictions to neurodevelopmental effects. Section 7 includes a discussion on an alternative approach based on hypothyroxinemia. Section 8 provides a short description of other potential adverse health impacts besides neurodevelopment that may be related to perchlorate exposure. Lastly, Section 9 presents the main conclusions for this report.

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2. Background on Thyroid Hormone Physiology and Connection to Neurodevelopment

In order to understand the approaches EPA is considering to inform future decisions including the derivation of an MCLG in accordance with the SDWA, it is first necessary to have a basic understanding of thyroid physiology (Section 2.1), including during pregnancy (Section 2.2), and pathophysiology (Section 2.3). It is also necessary to understand the mode of action by which perchlorate impacts thyroid hormone levels as put forward by the NRC (2005) and modified by the SAB (2013) (Section 2.4), how perchlorate is distributed and eliminated from the body (Section 2.5), and how thyroid hormones impact neurodevelopment (Section 2.6). Having this basic understanding of the mode of action through which perchlorate could impact thyroid hormone levels, and how thyroid hormones could in turn impact neurodevelopment, will provide a basis for understanding the approaches presented in this document.

2.1 Overview of Thyroid Physiology

The thyroid gland is part of a "self-regulating" loop referred to as the hypothalamic-pituitary-thyroid (HPT) axis (Figure 2), which controls metabolism, growth, brain development, and function (for review see Zoeller, Tan, & Tyl, 2007). Low circulating levels of thyroid hormones stimulate hypothalamic secretion of thyrotropin-releasing hormone (TRH), which diffuses into the anterior pituitary gland and stimulates the endocrine cells within the anterior pituitary (thyrotropes) to release TSH into the circulatory system. TSH acts on the thyroid gland to stimulate thyroid hormone uptake and production. Iodide is taken up from circulation by the NIS; serum iodide is transported into thyroid gland follicles for synthesis into the thyroid hormones T4 and to a lesser extent T3. Endocrine disruptors, such as perchlorate, could interfere with this process by directly inhibiting the uptake of iodide, thereby reducing the production of thyroid hormone.

T3 and T4 are formed when thyroglobulin (Tg; the precursor protein of T3 and T4) produced by the thyroid follicular cells is iodinated by the enzyme thyroperoxidase, and the iodinated protein is cleaved. T4 is generally thought to act as the prohormone for the more biologically active T3, which is required for normal development of the central nervous system in fetuses and in infants, as well as for ultimate skeletal development and growth. However, it should be noted that the regulatory factors that modulate the delivery of T4 to the fetus are not fully understood. Both T3 and T4 are critical determinants of metabolic function in humans of all ages. T4 and T3 are released into circulation, where they are primarily bound to the carrier proteins thyroxine-binding globulin (TBG), transthyretin (TTR), albumin, and lipoproteins (Di Cosmo et al., 2010; Kinne et al., 2015; Visser, Friesema, & Visser, 2011).

T3 and T4 in the blood that are bound to these proteins largely act as reserves because they are less readily metabolized in the liver and cannot enter cells unless in free form (Zoeller et al., 2007). However, in their free (or unbound) states (the free or unbound states of T4 and T3 are denoted as fT4 and fT3), both are available to be transported actively into specific cells. T4 is transported through the cellular membrane by specific transporters and transformed by deiodinases into T3, which is then transferred to the nucleus to cause transcriptional changes. Circulating T3 is mostly derived from peripheral monodeionization of T4 (Chanoine, Braverman, & Farwell, 1993; Peeters, 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

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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).

It is generally thought that changes in thyroid hormone levels that occur during pregnancy operate independently of changes in the set-point. For example, as the first trimester progresses, increases in human chorionic gonadotropin (hCG)[4] and thyroxine binding protein result in a higher blood concentration of T4 and can reduce TSH, making more fT4 available to the developing fetus (Morreale de Escobar, Obregón, & del Rey, 2007).

[4] hCG is a hormone produced during pregnancy by cells in the placenta (American Pregnancy Association, 2016).

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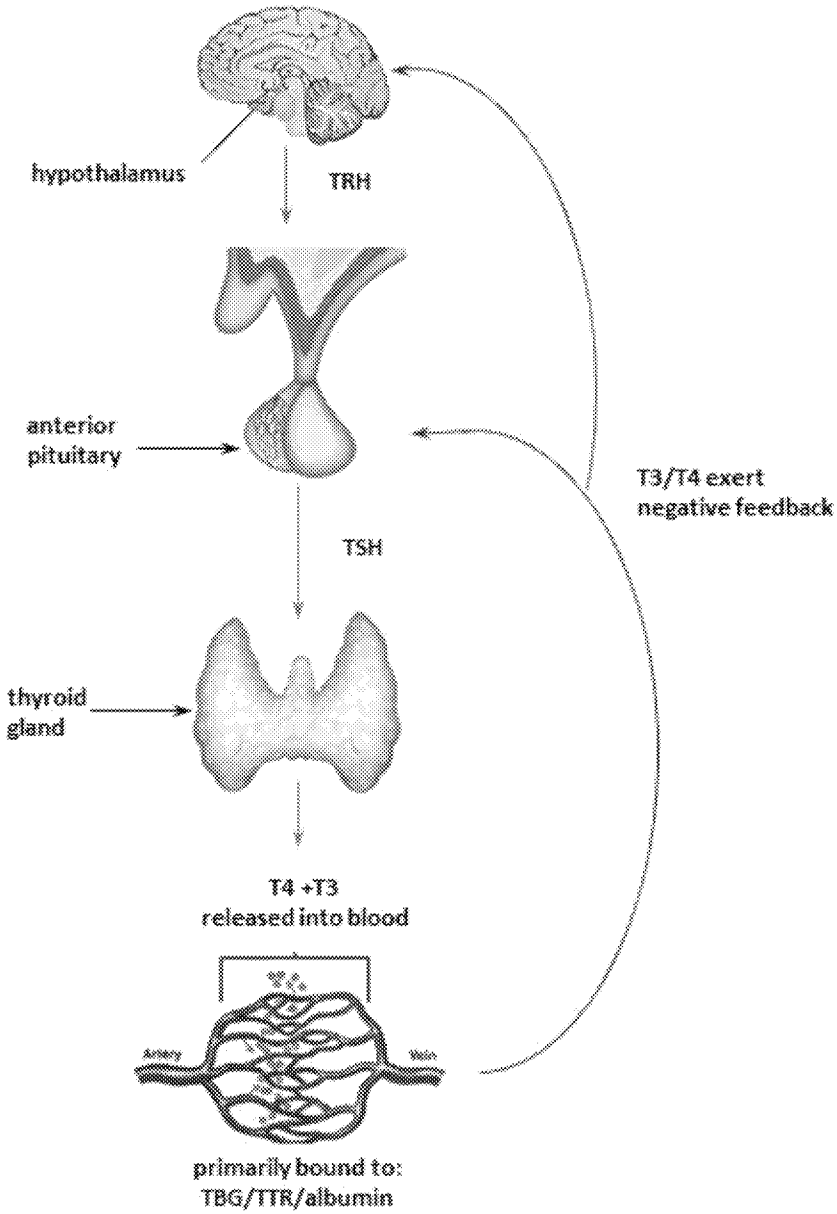
Figure 2. Summary of HPT Axis Showing Negative Feedback of Increased Circulating T4 and T3 on Hypothalamus and Anterior Pituitary



2.2 Thyroid Physiology in Pregnancy

In general, pregnancy requires the maternal thyroid gland to increase thyroid hormone production by around 50% (for review see Skeaff, 2011) to provide sufficient fT4 for fetal brain development. In the first trimester of pregnancy, this increased output of thyroid hormones is due to two specific processes. Specifically, estrogen increases during the first trimester, which increases the serum concentration of thyroid binding globulin (TBG), one of the main proteins to which T4 binds. The combination of increased TBG and hCG results in an increase in total T4 of about 50% over the pre-pregnancy level (Alexander et al., 2017). This increase in serum total T4 also increases serum fT4 during the first trimester, although fT4 levels fall over the next two trimesters (Alexander et al.,

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2017). The first-trimester increase in fT4 can lead in turn to a lower TSH concentration compared to the pre-pregnancy state.

Given the increased demand on the maternal thyroid in pregnancy, there is an increased demand for iodine to support additional hormone synthesis. If the maternal thyroid is fully functional, then sufficient dietary iodine intake will enable this to occur. According to the SAB, maternal 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. Although a fully functional system (i.e., in euthyroid individuals) can compensate with additional iodine consumption, hypothyroxinemic individuals are already compromised and iodine insufficiency can exacerbate this situation, putting the fetus at risk of neurological deficits (Dosiou & Medici, 2017; Negro, Soldin, Obregón, & Stagnaro-Green, 2011). 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) because the fetal thyroid gland is not formed until later in development. Conditions of low maternal iodine may also cause fetal thyroid function to be impacted once it begins, thereby putting the fetus at risk of hypothyroxinemia due to the lack of iodine coming from the mother to create its own thyroid hormone (Dosiou & Medici, 2017).

2.3 Thyroid Pathophysiology

Historically, the most commonly observed thyroid conditions have been goiter (i.e., enlarged thyroid gland) and congenital hypothyroidism. Hypothyroidism is defined as serum fT4 below and serum TSH above the reference range. Low serum fT4 may result from iodine insufficiency, from genetic disorders, autoimmune disease, cancer, pituitary insufficiency or environmental factors. The most common form of adult hypothyroidism results from an autoimmune thyroiditis (Hashimoto's disease) whereby a variety of cellular and antibody-related immune processes reduce thyroid hormone production within the gland (for review see Pyzik, Grywalska, Matyjaszek-Matuszek, & Roliński, 2015). Both post-partum thyroiditis and subacute lymphocytic (or silent) thyroiditis are considered subtypes of this disorder. Post-partum thyroiditis can occur in up to 5% of women and can involve periods of hyper- and hypo-thyroid activity (for review see Akamizu, 2015; Pearce, 2015b). Generally, the condition will resolve itself; however, as many as 20% of cases may lead to permanent hypothyroidism.

Hashimoto's disease can also be responsible for subclinical hypothyroidism where slight elevations in TSH are measured, but where T3 and T4 are within the population reference range. Subclinical hypothyroidism requires monitoring because some individuals will develop clinical hypothyroidism. Other related autoimmune hypothyroid conditions include primary thyroid atrophy (Ord's disease), which is characterized by thyroid atrophy through invasion by T-lymphocytes and is likely part of the continuum of hypothyroid conditions, rather than a separate disorder from Hashimoto's disease (Carlé et al., 2009). Viral or other infections can result in the painful condition of subacute granulomatous thyroiditis. This condition, like post-partum thyroiditis, is generally transient and requires only beta-blocker and non-steroidal anti-inflammatory drugs (NSAIDs) or steroid treatment to resolve. Although not common, pituitary disorders or tumors can also result in reduced thyroid function through reduction in TSH output.

Thyroid peroxidase antibodies (also referred to as anti-thyroid peroxidase antibodies or TPO Ab) are a marker for thyroid autoimmunity, a condition in which a person's immune system antibodies mistakenly target parts of the thyroid gland or thyroid proteins, according to the American

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Association for Clinical Chemistry (AACC) (2016). Thyroid autoimmunity leads to chronic inflammation of the thyroid, can cause tissue damage, and may disrupt thyroid function. The TPO Abs work against thyroid peroxidase, which is an enzyme that helps in the conversion and synthesis process of T4 to T3 via the oxidation of iodine (AACC, 2016).

2.4 Perchlorate's Impact on Thyroid Physiology

The NRC (2005) proposed a mode of action for perchlorate. Figure 3 is a reproduction of this mode of action modified to include hypothyroxinemia. Evaluating hypothyroxinemia as a result of perchlorate exposure is the mode of action that the SAB recommended EPA utilize in evaluating the MCLG for perchlorate. Figure 3 begins with exposure to perchlorate, which then leads to perchlorate in the bloodstream, followed by the inhibition of iodide uptake in the thyroid. The NRC concluded that these steps have all been observed in humans, and any subsequent steps or results are biologically possible, but have not been clearly demonstrated in humans. 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) demonstrated an association between high maternal perchlorate exposure and risk of low IQ in offspring.

In their review, NRC deemed the inhibition of iodide uptake in the thyroid to be a non-adverse effect, and concluded that the body's compensatory mechanisms would keep thyroid hormone levels within the population reference range (NRC, 2005). However, concerns have been raised regarding this conclusion given the lack of empirical evidence provided to support it (Ginsberg, Hattis, Zoeller, & Rice, 2007). The NRC did list subsequent biologically plausible steps that include the following: altered thyroid hormone levels (e.g., decreased T3 and T4, increased TSH; which has now been demonstrated in the epidemiologic literature), growth of the thyroid gland (e.g., thyroid hypertrophy and hyperplasia), and hypothyroidism (defined above). Hypothyroidism, deemed by the NRC to be the first adverse effect, could lead to abnormal fetal and child growth development, as well as metabolic disorders at all ages. Given the importance of a properly functioning thyroid for fetal and child growth (Forhead & Fowden, 2014), hypothyroxinemia may also be associated with abnormal fetal and child growth.

In the SAB report on approaches to derive an MCLG for perchlorate, the SAB indicates that "the mode of action of perchlorate toxicity is well understood" (SAB, 2013, p. 2). The SAB finds that "hypothyroxinemia (i.e., low levels of thyroid hormone) is a more appropriate indicator of the potential adverse health effects than the more pronounced decreases in thyroid hormone associated with hypothyroidism" (SAB, 2013, p. 2). Moreover, the "sensitive populations EPA should consider for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women" (SAB, 2013, p. 2). Thus this report is following SAB's recommendations.

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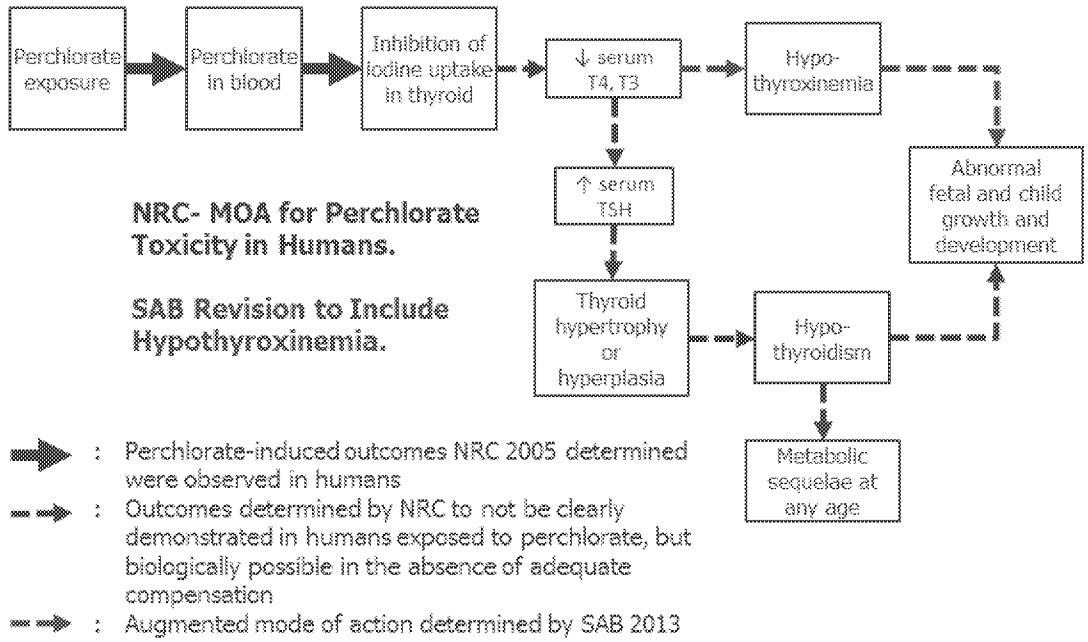
Figure 3. Modified Representation of NRC's Suggested Mode of Action for Perchlorate Toxicity in Humans Indicating First Adverse Effect in the Continuum of Perchlorate Exposure to Effect, Revised to Include Hypothyroxinemia as recommended by SAB



Source: Adapted from National Research Council (2005, Figure 5-2 (modified)).
Notes: Solid arrows represent outcomes that the NRC (2005) determined were observed in humans during perchlorate exposure. Black dashed arrows represent outcomes determined by the NRC (2005) to have not been clearly demonstrated in humans exposed to perchlorate, but that are biologically possible in the absence of adequate compensation. Blue dashed arrows represent the augmented mode of action from the SAB.

In addition to the NRC's proposed mode of action for perchlorate, it is also important to note that the interruption of iodide uptake by perchlorate creates a deficit that can accentuate the effect of other goitrogenic (i.e., goiter-causing) anions on the symporter. For example, Steinmaus, Miller, & Howd (2007) demonstrated that the combined effect of smoking and perchlorate is much greater than the effect of perchlorate or smoking on its own. Smoking cigarettes greatly increases an individual's exposure to thiocyanate, a known goitrogen. Thus, this upstream effect creates a vulnerability that increases the potential for chemical–chemical interaction (e.g., between perchlorate and other goitrogenic anions; or, between perchlorate and other anti-thyroid agents, such as polychlorinated biphenyls (PCBs)). It also increases the potential for chemical–nutritive status interaction (e.g., between perchlorate and low iodine intake), and perchlorate–physiological status interaction (e.g., between pregnancy, neonatal adaptation, aging, and disease status) in which the functional reserve of the HPT system is limited.

While perchlorate is expected to impair the production of T4 by the thyroid gland by competitively inhibiting the transfer of iodide into the thyroid gland, other environmental contaminants have been implicated as endocrine disruptors of other components of the HPT axis or plasma transport proteins. Multiple other chemicals, such as PCBs, polybrominated diphenyl ethers (PBDEs), bisphenol A, and perfluorinated acids (PFAs), also disrupt thyroid homeostasis (Butenhoff et al., 2002; Chang et al., 2008; Gauger et al., 2004; Moriyama et al., 2002; Van Rafelghem, Inhorn, & Peterson, 1987; Zhou, Taylor, DeVito, & Crofton, 2002; Zoeller, 2005). These disruptions occur through various

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mechanisms of action including directly affecting the thyroid's responsiveness to TSH (Bansal & Zoeller, 2008), affecting binding proteins (Chang et al., 2008; Melzer, Rice, Depledge, Henley, & Galloway, 2010), preventing NIS-mediated iodide uptake, and affecting expression of thyroid hormone-producing genes (Wu, Beland, & Fang, 2016). Bioaccumulation and co-exposures of persistent environmental contaminants can result in populations with high body burdens of contaminants that vary substantially with diet, region, gender, age, and body mass index (BMI). 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 hypothyroidism (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.

2.5 Distribution and Excretion of Perchlorate

Perchlorate salts such as ammonium, potassium, or sodium are highly water soluble and readily ionize in water. Once ingested, perchlorate is rapidly absorbed by the gastrointestinal tract and passed into circulation. In single-dose studies perchlorate has a short half-life of only 5–12 hours, but may be measured in urine within as little as 10 minutes to 3 hours after ingestion (Anbar, Guttmann, & Lewitus, 1959; Durand, 1938). Short-duration (two-week exposure) studies indicate a half-life of approximately 8 hours (Greer et al., 2002), with as much as 77% of the perchlorate being excreted per day with consumption of 0.14 mg/kg/day (Lawrence et al., 2000). A six-month low-dose study of healthy volunteers at 0.5 mg or 3.0 mg per day indicated daily excretion rates of 0.3 ± 0.07 mg/day and 2.1 ± 0.43 mg/day, respectively (Braverman et al., 2006), representing approximately 60% and 70% excretion of perchlorate per day. There is little to no metabolic conversion or catabolism of perchlorate ions prior to excretion.

The remaining perchlorate is transported by the NIS in the thyroid, kidney, gastric mucosa, salivary glands, placenta, mammary glands, and choroid plexus (Akturk et al., 2013; Spitzweg & Morris, 2002). Placental NIS plays a role in assuring adequate transfer of maternal iodide to the fetus by actively transferring iodide from the maternal blood circulation to the fetal blood circulation. Disruption of the supply processes, either due to low maternal T3/T4 levels, or by inhibition of the placental NIS by perchlorate, may further reduce fetal T3/T4 levels. Competitive inhibition of placental NIS by perchlorate could reduce uptake of iodide from the maternal circulation and reduce thyroid hormone production within the fetal thyroid gland. Further, once the fetus has a functional thyroid, inhibition of the fetal thyroidal NIS, as well as iodide deficiency from the blockade of the placental NIS, could result in additional reductions in fetal T3/T4 levels.

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). These *in vitro* observations may have implications for the placental transfer of iodide and perchlorate and subsequent fetal thyroid functions. As yet there is no direct evidence to indicate that the quantity of placental NIS is upregulated in response to increased TSH in the same way, or to the same extent, as seen in Tran et al. (2008). However, if this is the case, additional stimulation by maternal TSH in the presence of perchlorate may result in an absolute increase in NIS and subsequently increase perchlorate transfer to the placenta. 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),

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so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and increased perchlorate transfer.

Perchlorate, like thiocyanate, selenium cyanate, and nitrate, competitively binds, in a dose-dependent manner, to the NIS and reduces iodide uptake by the thyroid gland. Recent work using a non-linear regression model shows that the Michaelis-Menten constant (K_m), that characterizes the binding affinity of perchlorate for the NIS is approximately 0.59 μM, which is about 60% of that originally predicted (Schlosser, 2016). This means that approximately two-fold less perchlorate is required to out-compete iodide than suggested by earlier models. Since both iodide and perchlorate would be consumed during the day, changes in dietary intake, uptake, and competition between the two ions will vary depending on the foods consumed and water sources, and the rate of clearance of each ion from circulation.

2.6 Physiologic Connection between Thyroid Hormone Levels and Neurodevelopment

The profound effects of thyroid deficiencies during development were first documented in children with congenital hypothyroidism by Paracelsus (Cranefield & Federn, 1963). Modern studies demonstrate that unless treated, children with congenital hypothyroidism will suffer from problems associated with somatic growth and an array of visuomotor and neurocognitive deficits. Aberrant patterns of growth, development, and organization of the cortex, cerebellum, hippocampus, basal ganglia, and brain stem can all result from reduced thyroid hormone exposure during development (G. Williams, 2008; Zoeller & Rovet, 2004).

Thyroid hormones are essential for the development and differentiation of the developing brain. The brain and spinal cord begin development in the first half of the first trimester. fT4 passes through the blood-brain barrier via multiple, specific transporter proteins. Next, T4 is converted to T3 by the developing glial cells and then transported to neurons. T3 then interacts with nuclear receptors to tightly regulate gene expression so that neurogenesis, synaptogenesis, neuronal migration, cell differentiation, and myelination are developmentally appropriate. Deficiencies in thyroid hormones through iodine deficiency, congenital hypothyroidism, or maternal hypothyroidism/hypothyroxinemia can result in neurological impairments and intellectual deficits (Morreale de Escobar, Obregón, & Escobar del Ray, 2000).

The fetal thyroid gland first begins to concentrate iodide at about 11–12 weeks and begins significant contribution to fetal development around 16 weeks. However, the developing fetus still relies on some supply of maternal thyroid hormones, primarily fT4 until birth (Morreale de Escobar, Obregón, & Escobar del Rey, 2004). The fetal thyroid is not fully mature until birth, so premature birth can also be associated with low thyroid hormone concentrations. Thus, alterations in thyroid hormone levels can impact brain development in a variety of ways depending on when the alteration occurs and for how long.

For example, early 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,

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increases in hCG 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 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).

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). Additionally, there is also now emerging concern that there may be adverse effects associated with fT4 levels that are above the normal range (Korevaar et al., 2016).

Additionally, humans continue to undergo considerable post-natal brain development well through puberty and into early adulthood. A properly functioning HPT is necessary for proper neurologic development at this stage (Zoeller & Rovet, 2004). This is particularly true in the hippocampus, which is considered to have a relatively high degree of neuroplasticity in humans and undergoes considerable adult neurogenesis. How the behavioral and cognitive deficits associated with subclinical hypothyroidism and hypothyroxinemia are manifested within the brain is a research area where further evaluation is needed.

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3. Overview of EPA's Biologically Based Dose Response Model for Perchlorate's Impact on Thyroid Hormone Levels

EPA is proposing to inform the derivation of the MCLG for perchlorate by utilizing a BBDR model for early pregnancy to predict the impact that perchlorate will have on serum thyroid hormone levels at a given iodine intake (Step 1 of Figure 1). This section summarizes the history of the development of the BBDR model along with its current structure (Section 3.1). Further details are provided on key model parameters and attributes (Section 3.2 and Section 3.3), which is followed by a summary of results relevant to this analysis (Section 3.4). Lastly, there is a discussion of potential uncertainties associated with the model (Section 3.5). The BBDR model overview provided here is supported by detailed descriptions in Appendix A.

The BBDR model can be described as containing two main components: (1) a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of these two anions; and (2) 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, most significantly T4. The pharmacokinetic portion contains a physiological description (organ volumes, blood flows) and chemical-specific information (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 NIS) in association with a particular exposure scenario (route of exposure, age, dose level). This portion of the model is similar to other physiologically based pharmacokinetic models and for perchlorate is simplified by the absence of metabolism. The pharmacodynamic portion 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, BBDR modeling attempts to predict the internal dose of a chemical associated with a particular exposure scenario and the perturbation this internal dose can have on host systems.

3.1 Background and Structure of BBDR Model Development

In 2012, EPA sought advice from the SAB on how best to consider and interpret life stage information, epidemiologic and biomonitoring data, PBPK analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. In 2013, the SAB recommended the following (SAB, 2013):

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling (PBPK/PD);
- 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" (SAB, 2013, p. 19).

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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 FDA, first developed and integrated PBPK models for perchlorate and iodide with BBDR models for thyroid hormones to predict the effect of perchlorate on the thyroid gland in formula-fed and breastfed infants for the post-natal period from days 7 to 90, as well as lactating women and third-trimester pregnant women. This draft version of the developed model was intended to be valid for fT4 levels ranging from euthyroid to as low as hypothyroxinemia, in which fT4 levels are decreased to the lower end of the normal (i.e., within the population reference) range and TSH levels remain within the normal range (Silva & Silva, 1981). The model was limited to the range of perchlorate doses and dietary iodine intakes for which thyroid hormone levels are assumed to be maintained within a reference range without action of the TSH feedback mechanism.[5]

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

EPA considered all of the peer reviewers' recommendations 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 this section; additional detail is available in Appendix A. 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 distribution of thyroid hormone levels in the population, as well as the population median thyroid hormone levels; and conducting an uncertainty analysis for key parameters.

The BBDR model for which an overview is provided in this section and in Figure 4 is described in complete detail in Appendix A. In this model, EPA simulated the uptake and disposition of iodide and perchlorate and their competitive interaction at the NIS within the thyroid and elsewhere in the body.

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[5] For a more detailed discussion on the development of the draft model, its calibration, and dose-response evaluations, please see the 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 Analysis.* The report is available through the docket at http://www.regulations.gov *(Docket ID No. EPA-HQ-OW-2016-0439).*

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Based upon the availability of iodide, thyroid hormone synthesis, distribution, and metabolic transformation are modeled to yield predictions of blood levels of T4 and T3 (i.e., total T4, fT4, free T3, and total T3 (tT3)). Further, a TSH feedback loop has now been incorporated in which TSH levels are simulated based upon the predicted level of fT4 according to the relationship between those hormones as observed in humans. 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. The BBDR model was first developed for non-pregnant women and then extended to pregnancy by incorporating time-dependent parameters based on changes observed in early pregnancy through gestation week (GW) 16. It is 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. Appendix A includes sensitivity and uncertainty analyses of the updated model.

As described in Section 2.1, the decision to focus on early pregnancy was based on the fact that the epidemiology supporting the relationship between maternal thyroid hormone levels and subsequent neurodevelopmental outcomes is stronger for deficits in fT4 during the first trimester as opposed to later in pregnancy (e.g.,Pop et al., 1999, 2002). Given this focus on early pregnancy, the structure of the BBDR model is simplified from that of the previously described late-gestation model (previously reviewed in January 2017, based on Lumen et al., 2013), based upon the understanding that the fetal thyroid gland does not begin functioning until the second half of pregnancy. During early pregnancy, thyroid hormone-dependent neurodevelopment is driven by the supply of maternal thyroid hormone (in particular, serum concentrations of fT4) (Morreale de Escobar et al., 2004). Further, the epidemiology supporting this effect is stronger for first-trimester deficits in fT4 as opposed to later in pregnancy (Pop et al., 1999, 2002). In particular, the present model has been refined to focus on predicting maternal thyroid hormone levels during early pregnancy.

This model structure (Figure 4) is adapted from the third-trimester model of Lumen et al. (2013)[6] and the lactation iodide/thyroid hormone model of Fisher et al. (2016) with simplifications of some aspects and elaboration and adjustments of others. The model is comprised of sub-models for perchlorate, iodide, T4 and T3. The six-compartments used for perchlorate and iodide in the third-trimester BBDR model of Lumen et al. (2013) were condensed to essentially three compartments: plasma, thyroid and "rest of body" (ROB). This choice is justified because the fetus and its constituent compartments are much smaller in the first trimester and therefore it was deemed unnecessary to explicitly consider them. For example, at the end of the first trimester the fetus is expected to weigh less than 0.15 kg. To be clear, the placenta and fetus mass are included in the maternal ROB and condensation of other maternal compartments into one compartment is not

[6] During the development of this report, a study by Lumen & George (2017a) was published that extended the Lumen et al. (2013) model to include more severe iodine deficiency conditions, incorporate the effects of homeostatic mechanisms, and develop the extended model into a population-based model. Another study by Lumen & George (2017b) integrated the calibrated perchlorate exposure model from Lumen et al. (2013) into the population-based model in Lumen and George (2017a). Lumen and George (2017b) used Monte Carlo sampling and probabilistic simulation to quantify the distribution of urinary perchlorate for late-gestation pregnant women and to conduct an uncertainty analysis of influential perchlorate-specific parameters.

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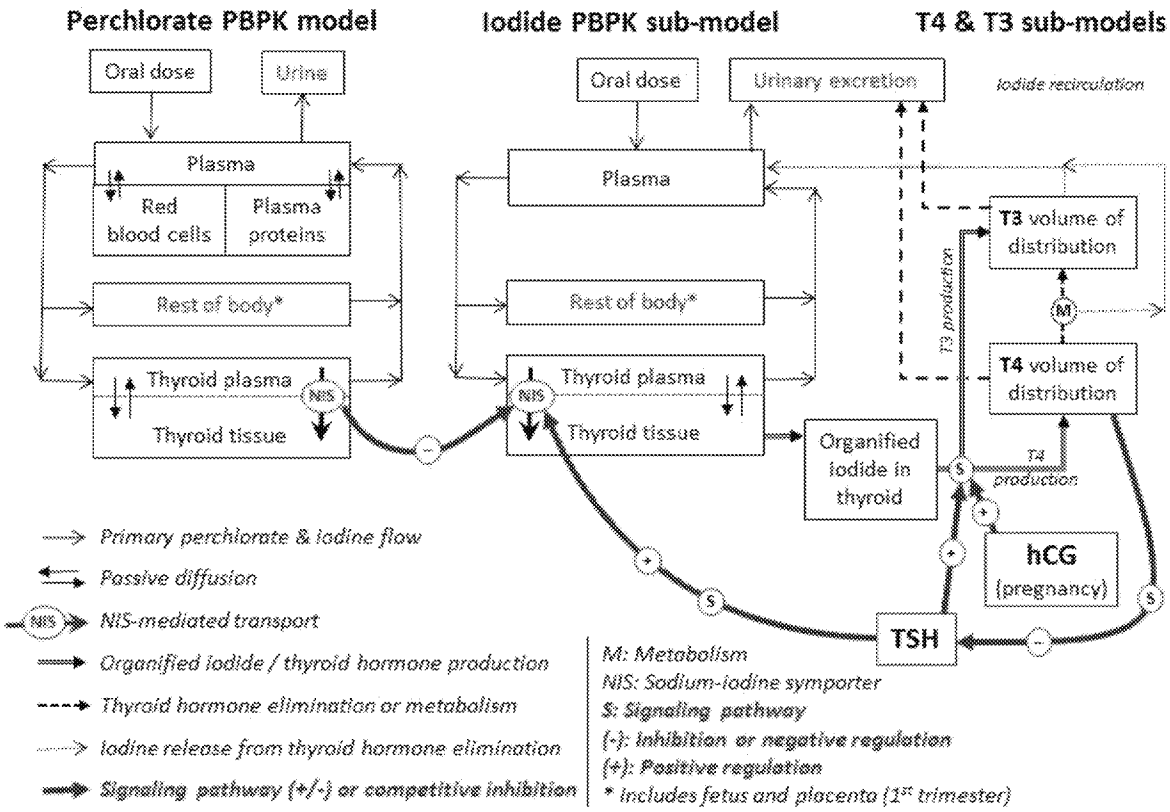
expected to significantly affect the predicted concentrations of the key anions and hormones given that they are described for long-term, continuous ingestion of iodine and perchlorate. Partitioning of perchlorate into red blood cells and binding to plasma protein are included in this model, unlike that of Lumen et al. (2013).

Figure 4. Overview of the Structure of the Early Pregnancy BBDR Model



The BBDR model is dependent on the known physiological mechanisms that occur in the thyroid as they relate to iodide and perchlorate exposure as summarized in Section 2 (for review see Zoeller et al., 2007). That is, within the iodide sub-model, iodide is consumed and enters the plasma. From the plasma, iodide can be transported to the thyroid. In the thyroid, T3 and T4 are formed when thyroglobulin (Tg; the precursor protein of T3 and T4) produced by the thyroid follicular cells is combined with iodide; this combined Tg-iodide is identified as "organified" or "bound" iodide in the model. Release of T4 and T3 into circulation is assumed to draw from this common thyroidal pool.

Because the model time-scale for changes in hormone levels is in weeks while variation in TSH is known to occur on a much faster time-scale, it was deemed unnecessary to explicitly describe the production, distribution and clearance of TSH. Instead, TSH is assumed to respond immediately to any changes in fT4, with TSH being a decreasing function of fT4: the higher the serum fT4 concentration, the lower TSH. The activity (Vmax) for NIS-mediated uptake of iodide (and perchlorate) by the thyroid and rate constants for production of T4 and T3 are then assumed to increase as TSH increases, leading to a negative feedback loop. However, the response of fT4 to this feedback is not instantaneous, since it takes time for an increased production rate to lead to increased circulating levels of fT4.

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While any decrease in fT4 leads to an increase in TSH, the relationship is nonlinear with less of a change in TSH per unit change in fT4 when fT4 is in the euthyroid range than outside of it, based on observational data. Likewise, increases in fT4 lead to decreases in TSH.

In addition to regulation by TSH, hCG levels rise in early pregnancy and this increases T4 production. (The Vmax for NIS-mediated uptake is also increased during pregnancy based on independent data, but that change is not described as an explicit function of hCG.) The stimulatory and feedback pathways are indicated by the thick, solid, red arrows (identified as "signaling pathways") in Figure 4. 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 inhibition 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 stimulation 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.

Subsequent sections describe key parameters in the model. Details regarding model calibration and the underlying mathematical functions of the sub-models are provided in Appendix A.

3.2 Summary of Key BBDR Model Parameters

The current BBDR model is built upon previous models of the thyroid for pregnancy (Merrill et al., 2005; Lumen et al., 2013) and lactation (Fisher, Wang, George, Gearhart, & McLanahan, 2016) with two major alterations for the current purpose: 1) adaptation for the non-pregnant woman and early pregnancy up to 16 GW; and 2) incorporation of the TSH feedback loop. EPA made various additional modifications in the process of examining the model code and fits to underlying data. Table 1 and the subsequent text provide an overview of key model parameters and describe both how these parameters were derived and how they may differ from previous versions of the model. This table does not summarize all the BBDR model parameters. A more complete accounting of all model parameters is provided in Appendix A.

Table 1. Summary of Major Features of Current BBDR Modeling

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
Iodide Sub-model	
Partition coefficient (PC) ROB: blood = (Prob_I) 0.243	The current model uses a weighted average of tissue-specific PCs for the new ROB compartment that is adjusted for NIS-mediated uptake in skin and mammary glands. The adjustment for the skin and mammary NIS increased the PC by 20%. Lumen et al. (2013) reported PCs for iodide for individual tissues that ranged from 0.15 to 0.4, which were used as-is in the January 2017 model.
Plasma protein binding of iodide = N/A	Not modeled in current BBDR model or January 2017.
Uptake into thyroid via NIS Thyroid Iodide Uptake (VmaxNISF_thy_I) = 690 nmol/h/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy); NIS affinity (KmNIS_I) = 31.5 µm	The current model uses the same saturable Michaelis-Menten approach specifying a scaled Vmax (VmaxNISF_thy_I) and K_m (KmNIS_I) for iodide, which is inhibited by perchlorate. Further, it uses the same K_m as used in the Lumen et al. (2013) model. The current model uses a 5.6-fold lower VmaxC compared to that in Lumen et al. (2013). This is based on fitting the data of female subjects from Greer et al. (2002). Further, VmaxC is scaled to increase

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Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
	with pregnancy based on an empirical relationship between gestational age and radioactive iodide uptake (see Appendix A).
Iodide from T4 and T3 deiodination based upon degradation rate of T4 (KdegT4F) and T3 (KdegT3F) KdegT4F = 1.9 x 10^{-5} L/hr/kg$^{0.75}$ KdegT3F = 1.7 x 10^{-4} L/hr/kg$^{0.75}$	The current model decreased KdegT4F and KdegT3F by a factor of 10 compared to the Lumen et al. (2013) values of 1.9 x 10^{-4} and 1.7x10^{-3} L/hr/kg$^{0.75}$, respectively. The decrease was used to enable fitting of the model to the range of NHANES data, given uncertainties in other model parameters, with the procedure used by EPA (see Appendix A, Section 2.2.3, for details). The current model uses the assumption from Lumen et al. (2013) that 50% of T4 degradation is due to T3 releasing one iodide ion, while the other 50% is completely degraded, yielding four iodide ions. The formula is: RdeiodT4=0.5(RdegT4 + 4*RdegT4) = 2.5*RdegT4 nmol/hr
Elimination to urine (CLFUI) = 0.0653 L/hr/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy)	The current model begins with non-pregnant clearance of CLFUI = 0.0653 L/hr/kg$^{0.75}$ and increases over pregnancy by an empirical relationship between gestational age and iodide clearance (see Appendix A). Lumen et al. (2013) assumed that iodine clearance was a function of iodine intake, with the relationship fitted to data from Dunn & Delange (2005) for the subjects from multiple studies (not necessarily during pregnancy).
Perchlorate Sub-model	
Partition coefficient (PC) ROB:serum = (Prob_P) 0.558	The current model uses a weighted average of tissue-specific PCs for the new ROB compartment and includes NIS uptake in skin and mammary glands. The inclusion of the skin and mammary NIS increased the PC by 80%. Lumen et al. (2013) reported PCs for perchlorate for individual tissues that ranged from 0.13 to 0.56.
Plasma protein binding (Km_Bp) = 0.181 μM	Included in the current model; not included in Lumen et al. (2013).
Distribution into red blood cells (RBCs), RBC:serum PRBC_P = 0.8	Included in the current model; not included in Lumen et al. (2013).
Uptake into thyroid via NIS (VmaxNISF_thy_P) = 650 nmol/h/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy); (KmNIS_P) = 0.489 μM	The current model uses a K_m 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, K_m is the 2.5th percentile lower confidence limit of the population median based upon EPA 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).
Elimination to urine (CLFUP) = 0.105 L/hr/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy)	The current model uses a higher urinary clearance compared to the clearance used in the Lumen et al. (2013) model (i.e., 0.05 L/hr/kg$^{0.75}$). The current model's clearance rate, CLFUP = 0.105 L/hr/kg$^{0.75}$, is for non-pregnant women and based on EPA reanalysis of Greer et al. (2002); it is the 2.5th percentile of the sampling distribution for the population median (see Appendix A), with the 50th percentile being 0.122 L/hr/kg$^{0.75}$. Urinary clearance increases over pregnancy by an empirical relationship between gestational age and glomerular filtration (see Appendix A). Lumen et al. (2013) fit a perchlorate clearance to Chilean (Téllez Téllez et al., 2005) pregnant women based upon estimated water intake. There were no data for dietary exposure in Téllez Téllez et al. (2005), so Lumen et al. (2013) effectively assumed zero dietary contribution to

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Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
	total exposure in their analysis.
T4 Synthesis	
Production of T4 (KProdT4F) = $5.83*10^{-7}$ L/hr/kg$^{.75}$ (non-pregnant value; this is scaled for 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 $5.83*10^{-7}$ L/hr/kg$^{0.75}$, which is lower than 2.45×10^{-6} used by Lumen et al. (2013) based on fitting to data of Nicoloff, Low, Dussault, & Fisher (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): $hCG_{reg} = 1 + 0.00354 \times hCG$.
TSH Feedback Loop	The current model incorporates a TSH feedback loop that adjusts the Vmax for uptake into the thyroid and production rate constants for T4 (KProdT4F) and T3 as TSH falls below or rises above its calibration point (i.e., the population percentile of TSH assumed to be consistent with the population percentiles of other thyroid hormones used for a particular calibration), in inverse relationship to corresponding increases or decreases in fT4. For example, when the model is calibrated to match median T4, T3, fT4, and fT3 levels, the median TSH level is selected as the calibration point, and regulation occurs as TSH goes above or below this level, in response to variation in fT4. The relationship between TSH and fT4 is explained by data in Hadlow et al. (2013) and further described below and in Appendix A. Lumen et al. (2013) did not have a TSH feedback loop.
T4 Distribution	
T4 Volume of Distribution (VDFT40) = 0.162 L/kg (non-pregnant value; this is scaled for pregnancy)	The current model has a baseline value (0.162 L/kg) for non-pregnant women that is scaled to decrease linearly with gestation time through GW 16 based upon a study that measured the distribution of radio-labelled T4 in pregnant and non-pregnant women. See Appendix A for additional details. The absolute volume of distribution is VDT4 = VDFT40*BW, so the decrease in the relative volume is somewhat offset by increasing BW. Lumen et al. (2013) used an estimate of 0.11 L/kg for the third trimester.
Free (fT4) to tT4 Ratio (FRT40) = 1.03×10^{-4} (non-pregnant value; this is scaled for pregnancy)	The current model uses a baseline value of 1.03×10^{-4} for median non-pregnant women and then estimates the ratio during pregnancy based on an empirical relationship derived from the ratio by gestational week. This relationship is based upon six studies as shown in Appendix A. Lumen et al. (2013) estimated that the fraction of total T4 converted to fT4 was approximately 9.0×10^{-5}.
T4 Degradation	
KdegT4F = $1.9*10^{-5}$ L/hr/kg$^{0.75}$	T4 degradation in the current model was selected to allow model calibration to the range of thyroid hormone values in NHANES as described above in the iodide sub-model section.
Additional Adjustments for Early Pregnancy	
Removal of placental and fetal compartments and condensing of maternal system to three compartments: serum, thyroid and ROB	Simplification of BBDR model structure from Lumen et al. (2013); see Figure 4 and related adjustments to PCs, compartment volume, and flows.
fT4: total T4 median serum concentration ratio, modeled to vary during early	A polynomial regression for fT4 fit to five datasets describing initial increase and then decrease of fT4 during early pregnancy was divided by a Hill equation

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Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
pregnancy	regression fit to five data sets describing the increase in total T4 during the first trimester. The resulting time-dependent fT4:T4 ratio (change vs. non-pregnant), which occurs due to increases in serum binding proteins, results in a decrease of approximately 30% in the fT4:T4 ratio during early pregnancy
Note: This table does not summarize all the BBDR model parameters. A more complete accounting of all model parameters is provided in Appendix A.	

3.3 Overview of Key Model Attributes That May Impact Thyroid Hormone Production

As described in Table 1, the baseline non-pregnancy rate for T4 synthesis was developed by fitting NHANES 2007-2012 median, 10th, and 90th percentile data for non-pregnant women, with adjustment for increasing T4 production and varying fT4:T4 ratios during early pregnancy as seen in a number of studies (see Appendix A and related references (e.g., La'ulu, 2011; Medici et al., 2012; Soldin et al., 2004; Stricker, 2007; Yan et al., 2011; Zhang et al., 2016)). There are several regulatory controls in the BBDR model that can impact T4 and T3 production, such as the inclusion of hCG in the model, varying iodine intake, and also the TSH feedback loop. The impact of hCG on T4 production is discussed in Table 1. Further details regarding how low iodine intake and the TSH feedback loop were considered in calibrating the model are presented below.

3.3.1 Low Iodine Intake

Plots of NHANES 2007-2012 data for non-pregnant women demonstrated little relationship between iodine intake and fT4, except possibly for iodide intake levels below 75 µg/day. Given limited data in this range, EPA 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). 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).

3.3.2 TSH Feedback Loop

TSH increase in response to decreases in T4 has been captured in numerous studies that document the inverse relationship between these hormones. A compilation of data describing this relationship (Hadlow et al, 2013) has been analyzed by EPA in Appendix A to enable TSH feedback loop incorporation into the BBDR model. The following equation elevates TSH in response to a lowered concentration of fT4, as might arise from goitrogen exposure or lowered iodine intake:

$$TSH(CfT4) = \frac{TSHtar \times TSHhad(CfT4)}{TSHhad(CfT4tar)}$$

In this equation, TSHtar is the "target" level of TSH in a population (percentile) or an individual corresponding to a given fT4 concentration (e.g., the median) in that population percentile or individual and TSHhad(CfT4) is the empirical function fit to the collected fT4 and TSH data by Hadlow et al. (2013). For example, the median TSH concentration from NHANES data is associated with the median fT4 for the same population; so these two would be CfT4tar and TSHtar for the presumed median individual. Using that pair of values in the TSH equation above scales

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TSHhad(CfT4) such that when CfT4 = CfT4tar, TSH(CfT4) = TSHtar. This combination of target hormone levels is the set point where both are stable and TSH will not increase or decrease thyroid activity beyond the corresponding fT4 value. When fT4 concentration decreases TSH(CfT4) increases. The ratio, TSH(CfT4)/TSHtar, determines the degree to which the BBDR model will upregulate iodide uptake and T4 production (i.e., if TSHhad(CfT4) > TSHhad(CfT4tar)). The result is that the change in fT4 from the set-point (CfT4tar) will be less than would occur in the absence of TSH feedback, but there will still be some change, hence a dose-response due to perchlorate.

The BBDR model achieves this feedback regulation by tuning three parameters, NIS Vmax (VmaxNISF_thy_I; i.e., modulation of number of symporter sites), KProdT4 (modulation of T4 synthesis rate), and KProdT3 (modulation of T3 synthesis rate). These three parameters are assumed to vary as $(TSH(CfT4)/TSHtar)^{pTSH}$, where the coefficient pTSH determines the strength of TSH stimulation. However, to estimate the value of pTSH one would need measurements of TSH and the thyroid-specific parameters which TSH is presumed to regulate – the Vmax for iodine uptake and the T4 and T3 production rate constants (the relationship between T4 and T3 production and thyroid iodide stores). Such data are not available for humans, so a nominal value of pTSH = 1 was tested. Using this value, model predictions appear to be consistent with median NHANES data for non-pregnant women (see section 3.2.3 in Appendix A), but a lower bound of pTSH = 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5th percentile value from NHANES (non-pregnant women), was used to obtain the dose-response results used for MCLG derivation (details in Appendix A). 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. TSH increases can drive corresponding increases in iodide uptake and T4 and T3 production as long as iodide supply is sufficient. With increasingly low iodide intake, colloidal iodide stores are modeled to decline, which ultimately impairs the thyroid's response to elevations in TSH.

3.4 Results of the BBDR Model

The BBDR model can predict serum thyroid hormone levels at specific gestational weeks, given levels of iodine intake and doses of perchlorate. Figure 5 displays plots that illustrate specific outputs of the model. The upper- and lower-bound simulations in this figure were developed using corresponding parameter sets for the median, upper, and lower bounds of fT4, T4, fT3, T3, and TSH. They are not true bounds, but are instead estimates for fT4 or TSH given NHANES data with median, 2.5th, and 97.5th percentiles for fT4, TSH, etc.

Table 2 and Table 3 summarize output of the BBDR model for various doses of perchlorate and gestational weeks and resulting fT4 and TSH levels at the median iodine intake (170 µg/day) and a low-iodine intake, respectively. In both cases the model is calibrated to match median thyroid hormone levels given an ingestion of 90 µg/day iodine – the median population as described in Appendix A. However, a weak level of TSH signaling strength, pTSH = 0.398, was used to illustrate the more sensitive dose-response from using that estimated lower bound. For analysis of a low iodine population an iodine intake level of 75 µg/day was selected. This intake level represents between the 15th and 20th percentile of the population distribution of estimated iodine intake from NHANES. EPA considered conducting the analysis at the lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. However, at 50 µg/day of iodide, the

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BBDR model predicts TSH levels which would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[7] (TSH ranges between 4.51 and 5.41 mIU/L at zero dose of perchlorate when evaluating gestational weeks 12, 13 and 16). In contrast, 75 µg/day iodine intake is associated with fT4 stores in the thyroid (Delange et al., 2000) and BBDR-modeled concentrations of serum fT4 and TSH that are significantly reduced from the population median but are still within the euthyroid range. This comports with the goal of evaluating perchlorate effects on neurodevelopment when starting with a population of pregnant women who are borderline hypothyroxinemic.

As described in Sections 5 and 6, the identified epidemiological literature led EPA to select gestational weeks 12, 13, and 16 for analysis. Results from the BBDR model output are subsequently summarized for these gestational weeks.

[7] For purposes of this analysis EPA evaluated the American Thyroid Association's (ATA) 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." ATA goes on to state, in the absence of population- and trimester-specific references ranges defined by a provider's institute or laboratory, 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 a. (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 GW 15 and 16) to determine the presence of hypothyroidism.

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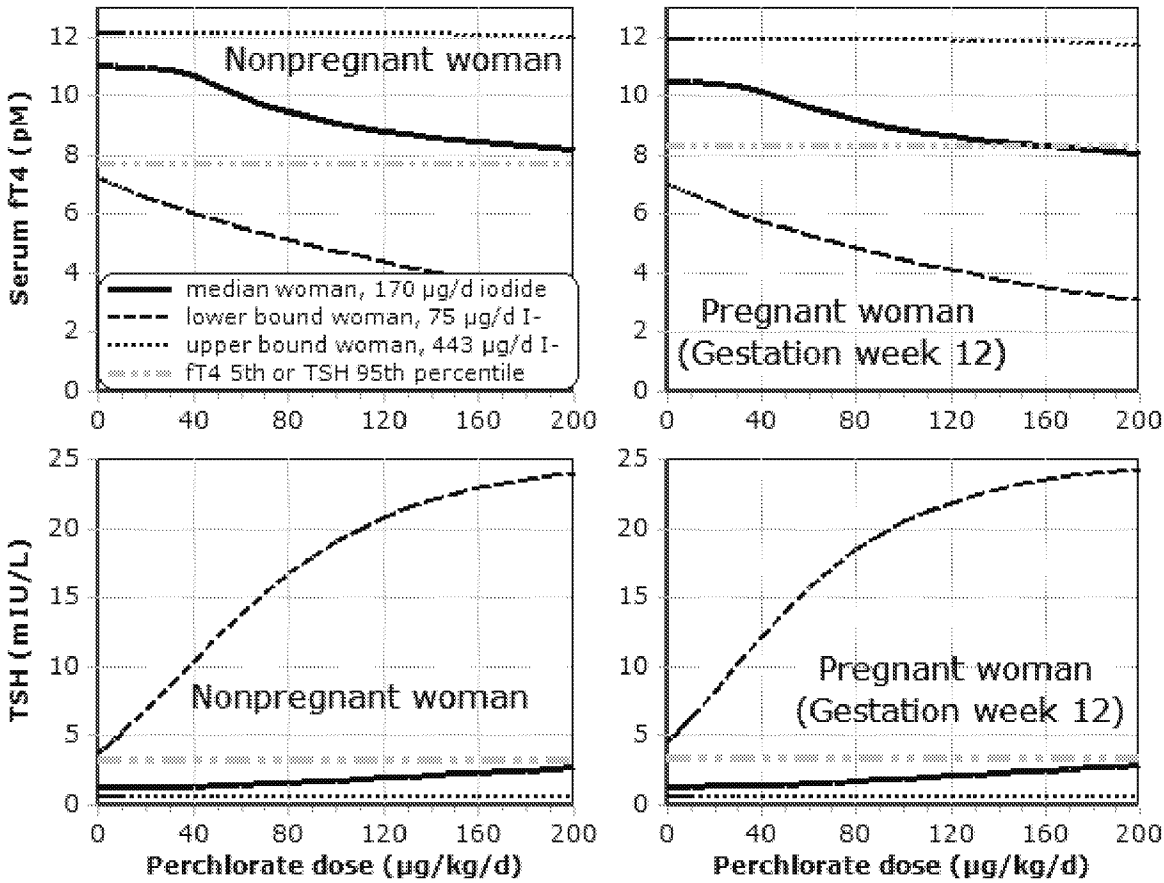
Figure 5. Example Output from the BBDR Model[a]



[a] BBDR model simulations using parameter sets calibrated for median (black, solid curve), lower bound (black, dashed curve), or upper bound (black, dotted curve) fT4 levels, as described in Appendix A. TSH levels used for calibration were assumed to be inverseley correlated with fT4, hence the lower bound level of TSH is associated with upper bound fT4 and vice-versa. Median and 90 µg/d percentile estimated iodine (I-) intake levels (170 and 443 µg/d, respectively) were used for simulations of median and upper bound women. An iodine intake of 75 µg/d was used for the lower bound woman, as described in the preceding text. Grey dash-dot lines show the 5th percentile of the estimated fT4 and upper bound for TSH, defining those boundaries of the euthyroid range.

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Table 2. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate (µg/kg/day) at Specified Gestational Weeks (GW) for 170 µg/day Iodine Intake[a]

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L) (% Change from 0 Dose)			TSH (mIU/L) (% change from 0 Dose)		
	GW 12	GW 13	GW 16	GW 12	GW 13	GW 16
0	10.67	10.64	10.25	1.35	1.35	1.40
1	10.66 (-0.04%)	10.64 (-0.05%)	10.24 (-0.06%)	1.35 (0.04%)	1.35 (0.04%)	1.40 (0.08%)
2	10.66 (-0.09%)	10.63 (-0.10%)	10.23 (-0.13%)	1.35 (0.07%)	1.35 (0.08%)	1.41 (0.15%)
3	10.65 (-0.13%)	10.63 (-0.14%)	10.23 (-0.19%)	1.35 (0.11%)	1.35 (0.12%)	1.41 (0.23%)
4	10.65 (-0.17%)	10.62 (-0.19%)	10.22 (-0.26%)	1.35 (0.15%)	1.35 (0.17%)	1.41 (0.31%)
5	10.64 (-0.22%)	10.62 (-0.24%)	10.21 (-0.32%)	1.35 (0.18%)	1.35 (0.21%)	1.41 (0.39%)
10	10.62 (-0.46%)	10.59 (-0.51%)	10.18 (-0.66%)	1.35 (0.39%)	1.36 (0.45%)	1.41 (0.82%)

[a] Results using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

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Table 3. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate (µg/kg/day) at Specified Gestational Weeks (GW) for 75 µg/day Iodine Intake[a]

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L) (% Change from 0 Dose)			TSH (mIU/L) (% Change from 0 Dose)		
	GW 12	GW 13	GW 16	GW 12	GW 13	GW 16
0	8.85	8.84	8.56	1.95	1.95	2.22
1	8.78 (-0.80%)	8.77 (-0.79%)	8.49 (-0.74%)	2.00 (2.94%)	2.01 (2.92%)	2.29 (3.25%)
2	8.71 (-1.56%)	8.71 (-1.54%)	8.43 (-1.46%)	2.06 (5.96%)	2.07 (5.92%)	2.36 (6.59%)
3	8.65 (-2.29%)	8.64 (-2.26%)	8.37 (-2.14%)	2.12 (9.07%)	2.13 (9.01%)	2.44 (10.02%)
4	8.59 (-2.98%)	8.58 (-2.95%)	8.32 (-2.79%)	2.18 (12.26%)	2.19 (12.18%)	2.52 (13.54%)
5	8.53 (-3.64%)	8.52 (-3.60%)	8.27 (-3.42%)	2.25 (15.53%)	2.25 (15.44%)	2.60 (17.15%)
10	8.27 (-6.56%)	8.27 (-6.52%)	8.03 (-6.22%)	2.59 (33.06%)	2.60 (32.94%)	3.02 (36.37%)

[a] Results using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

Figure 5 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. Increased urinary clearance of both iodide and perchlorate during pregnancy, described by the model, have the conflicting effect of both reducing iodide availability in the mother and reducing perchlorate blood concentration, so these two components of pregnancy-related changes will cancel each other out to some extent. The similarity in dose-response also reflects the assumption that the small placental and fetal compartments, with the fetal thyroid only just becoming active at the end of the first trimester, will have very little effect on maternal anion and thyroid hormone concentrations, which lead to the choice of a simplified model structure (Figure 4). Further, 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. 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.

On the contrary, the BBDR model predictions for perchlorate's effect on fT4 are much less than the impact of decreased intake of iodine from 170 to 75 µg/d on fT4. For example, in the low-iodine

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intake individuals there is predicted to be about a 6 to 6.5% drop in fT4 with 10 μg/kg/day exposure to perchlorate. 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 μg/kg/day.

3.5 Uncertainties Associated with the BBDR Model

The BBDR model allows for the evaluation of perchlorate effects on circulating levels of fT4 based upon interaction at the thyroidal NIS before and during early pregnancy at various iodine intakes. Being biologically based, the model aims to simulate a complex physiological process that has been relatively well studied, the HPT axis. Interest in how perchlorate may perturb this system has spurred development of this modeling framework to predict such influences. Given the complexity of the model there can be uncertainties in many different aspects, ranging from structural and functional relationships to specific parameter values for early pregnancy. McClanahan et al. (2009) examined an earlier version of the model against data in rats exposed to high-dose perchlorate with the conclusion that the model under-predicted the degree of T4 decline and TSH rise. Given differences across species in thyroid storage of iodide and set points, and the effects of high versus lower dose perchlorate, the previous validation effort does not necessarily reflect on the predictive capacity of the current model. However, it does highlight the lack of useful calibration and validation data for this BBDR modeling effort.

On the pharmacokinetic side of the model, the sub-models for iodide and perchlorate have been extensively developed and revised in the past (Merrill et al. 2005; Clewell et al. 2007; Lumen et al. 2013), although, as pointed out in McLanahan et al. (2014), there are very few calibration data for perchlorate kinetics in humans, particularly at the life stage of interest. This may be of particular importance given that available biomarker data to relate perchlorate external dose to internal serum concentration are highly variable and uncertain. For example, the Lumen et al. (2013) model was based on pregnant women living in a Chilean city with high levels of perchlorate in drinking water (Telléz Telléz et al. 2005). In that study, the standard deviation of the concentration of perchlorate in urine was similar to, or in one instance, greater than the mean urinary perchlorate concentration, indicating extreme variability. Furthermore, data used in the calibration from the Chilean city in Telléz Telléz et al. (2005) did not reflect a low-iodine intake population. Urinary iodide for the 37 subjects at the second prenatal visit was, on average, 217 μg/L, with a standard deviation of 109 μg/L. Other toxicokinetic factors that may affect the concentration of perchlorate at the thyroidal NIS include the extent of protein binding, the perchlorate urinary excretion rate, and the partitioning into non-thyroidal compartments (i.e., the ROB compartment). However, of these three, only perchlorate urinary clearance effects the long-term average concentration of perchlorate at the thyroidal NIS predicted by the BBDR model, and given the half-life of iodine in the thyroid, it is this long-term average that determines the effect on thyroid hormone levels.

At steady state, or under long-term continuous exposure conditions, the (average) free concentration of perchlorate in plasma is independent of the fraction bound to protein. An increase in the concentration of binding proteins will result in a temporary decrease in the free perchlorate concentration, resulting in a lower clearance rate to urine. Due to the lower clearance, there will then be an increase in total blood perchlorate concentration over a relatively short time (since exposure is ongoing) with urine clearance increasing in proportion to the free concentration and the amount bound to proteins also increasing, until steady state is again achieved with the free concentration returning to the same level as before the change in plasma proteins. The amount bound to proteins

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will then be increased in proportion to the increase in binding protein concentration. Likewise a drop in binding proteins will cause a short-term increase in free perchlorate concentration, but this concentration will quickly return to the same steady-state level as before the protein level change as the amount bound to protein declines. Since such short-term fluctuations have minimal impact on the organified iodide in the thyroid, they are not significant to the overall dose-response.

There is some uncertainty due to the assumption that the concentration (and accumulation) of iodide and thyroid hormones in the placenta and fetus, and fetal metabolism of thyroid hormones, is not significantly different from the rest of the maternal body. For example, if the fetus and placenta are 2% of total maternal BW at a given point in gestation, and the amount of iodide accumulation or T4 metabolism in them is actually twice the average for the rest of the mother's body, the impact of neglecting that difference would only be a change of 2% in predicted maternal concentrations. The total rate of iodide accumulation or T4 metabolism in the fetus (not the rate per kg fetal BW) would have to be a significant fraction of the total maternal ingestion rate for iodide, or total maternal T4 metabolism and clearance, in order for the such differences in the fetus to directly impact the maternal levels. (The model already accounts for the effects of hCG and changes in maternal physiology.) Hence the uncertainty from not including explicit placental and fetal compartments is determined by the uncertainty in the assumption that iodide accumulation and thyroid hormone metabolism are limited in early gestation.

The effect of the interaction between perchlorate and thiocyanate on thyroid hormone status seen in two epidemiology studies (Steinmaus et al. 2007; 2013) has been assumed to be due to a combined inhibitory effect on the NIS, but thiocyanate is also a competitive substrate for the thyroid peroxidase, a mechanism independent of perchlorate. 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. 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.

The composite partition coefficient (PC) for perchlorate in ROB of 0.558 is considerably higher than that for iodide (0.243). Both perchlorate and iodide are subject to NIS-mediated uptake into mammary glands and skin, which is accounted for in the relevant partition coefficients. 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. But as noted above, this distribution will not impact the long-term average free serum concentration of perchlorate which determines the effect on thyroid hormones.

A key pharmacokinetic factor is the perchlorate renal elimination rate, which is an influential parameter in the fitting procedure of Lumen et al. (2013), who attempted to match BBDR model predictions to biomarker measurements in pregnant Chilean women. However that estimation assumed that perchlorate exposure was only in drinking water, with none coming from diet. When exposure is significantly under-estimated, a low level of urinary clearance would be required to match an observed serum concentration since the rate of absorption into the body is under-estimated. The current modeling effort for early pregnancy uses an excretion rate that is more than twice that of the third-trimester Lumen et al. (2013) model. Merrill et al. (2005) estimated a urinary excretion rate

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(0.11 L/hr/kg$^{0.75}$) that is similar to what is used presently to represent the non-pregnant state, and this was based upon mean urinary perchlorate concentrations measured in the Greer et al. (2002) study. Evaluation of the variability in perchlorate urinary excretion in available human datasets is presented in Appendix A.

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. A recent version of the BBDR model recalibrated for greater perchlorate affinity of the NIS (Schlosser, 2016) was able to simulate the dose response for perchlorate's effect on radioiodide uptake seen in Greer et al. (2002). That correspondence builds confidence in the BBDR model's ability to simulate current data informing the user of perchlorate toxicokinetics and toxicodynamics in humans. However, the Greer et al. (2002) study was short-term, and did not evaluate the iodine intake status, smoking status, or intake of other goitrogens in volunteers, which may affect the ability to detect low-level perchlorate effects in population studies. Greer et al. (2002) used radioiodide uptake data from each subject as his/her own control, implicitly assuming that the impact of these other factors did not change over the weeks during which the study was conducted. 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. 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.

Data for perchlorate effects on circulating hormone levels that might be used for model evaluation are very limited. Clinical toxicology and occupational studies in high-dose subjects showing minimal changes in thyroid hormone levels (Braverman, 2007) are discordant with general population epidemiology studies at much lower exposures that show associations between urinary perchlorate, TSH increases, and T4 (or fT4) decreases (Blount et al., 2006; Braverman, 2007; Steinmaus et al., 2016). Given the limited data available for model evaluation, perchlorate toxicokinetics and toxicodynamics in pregnancy remain a source of uncertainty. This could impact the resulting fT4 predictions of neurodevelopmental effects. As an example, a comparison analysis of the BBDR model to predicted fT4 and TSH changes using the epidemiology literature (i.e., Steinmaus et al., 2016) is provided in Appendix B. This analysis used Steinmaus et al. (2016) to evaluate the relationship between perchlorate exposure and fT4 and TSH. When considering the median iodine intake, the changes predicted by the BBDR model for TSH are smaller than that predicted by Steinmaus et al. (2016), even when compared to the predictions based on the lower beta estimate from the 95% CI. However, when comparing the BBDR model's low-iodine TSH changes to those predicted by Steinmaus et al. (2016), they are closer in magnitude to the lower effect estimates and steadily increase to greater predicted changes as doses increase. In evaluating the results for fT4, in all instances the BBDR Model predicts a smaller change than that projected by the Steinmaus et al. (2016) slope. The closest match, especially at lower perchlorate doses, is between the low-iodine runs of the BBDR model and the low estimate of the Steinmaus et al. (2016) slope. In addition, an approach to assess changes in IQ as a result of changes in perchlorate exposure using Steinmaus et al. (2016) is provided in Appendix C.

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Incorporation of the TSH feedback loop in the model introduces other uncertainties. This is because, as discussed in Fitzgerald and Bean (2016), increasing TSH levels do not have a consistently predictable impact on T4 levels. Fitzgerald and Bean (2016) conclude that their mathematically derived curves describing the T4 response to TSH "implies greater inter-individual variation in the positive thyroid T4 response to TSH than in the central inhibitory TSH response to T4." 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. The strength of the TSH stimulatory effect is varied in model predictions to account for such variability, and the results in Table 2 and Table 3, for example, are from assuming pTSH = 0.398, i.e., a stimulatory effect ~ 60% lower than pTSH = 1 or direct proportionality, which otherwise appears to fit population median data reasonably well. Either using the weak or a stronger stimulatory term, the feedback does not maintain fT4 concentration exactly at the set-point or target. Any exposure to perchlorate is predicted to reduce fT4 to some extent. The TSH feedback only reduces the dose-response compared to what is predicted without the term.

As mentioned above, the potential for perchlorate to interact with other goitrogens has been documented with respect to thiocyanate and tobacco smoking (Steinmaus et al., 2013; Steinmaus et al., 2007). As in the case with the low-iodide analysis of Blount et al. (2006), the interaction with thiocyanate was most evident in a nested design in which the vulnerable population of smokers could be evaluated separately from the remainder of the population (Steinmaus et al., 2013). 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. Currently, the vulnerability introduced by other goitrogens' interactions with perchlorate at the NIS or on fT4 population distributions remains a source of uncertainty that could impact the resulting fT4 predictions of neurodevelopmental effects. The current BBDR model and analysis assume that exposures to perchlorate and other goitrogens vary independently in the population and that the effects are additive.

Investigation of the effect of perchlorate on iodine transport by the NIS *in vitro* (Kosugi et al., 1996) and revised mathematical analysis by (Schlosser, 2016) indicate that this effect is consistent with classical competitive inhibition of the transporter. An equation describing this competitive inhibition is provided in Appendix A, Section 1.2.2. Based on this mechanism, and the simple pharmacokinetics of perchlorate (no metabolism, ~ 100% urinary excretion), it is assumed that there is minimal additional uncertainty in extrapolating the effect of perchlorate on iodide uptake downward from the middle perchlorate exposure levels used by Greer et al. (2002) (i.e., 20 and 100 μg/kg/d) to lower exposure levels relevant to MCLG derivation and/or human environmental exposures. The various uncertainties discussed above and in Appendix A do apply to low-dose extrapolation, but based on this mechanistic understanding there should be no magnification of uncertainty at low doses. The

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model is likely to become more uncertain when extrapolating to higher exposure levels, where mechanisms not included in the model may become active.

Lastly, the potential for perchlorate to interact with pre-existing thyroidal diseases and conditions is a source of uncertainty. The BBDR model presented here is intended to describe an otherwise healthy (euthyroid) woman during the period extending from several years before pregnancy through gestation week 16. 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 results in reduced production of T4 (Poplawska-Kita et al., 2014; Yamazaki et al., 2007). The ATSDR Toxicological Profile for Perchlorate (2008) states that individuals with Hashimoto's Disease and exposure to perchlorate have relatively poor thyroid function, while Brent (2010) raises the possibility that perchlorate and similar environmental exposures could increase the risk for Hashimoto's Disease. To the extent that such conditions or pre-conditions cause additional interference with iodide uptake and deplete colloidal stores of iodide, this may set the stage for a toxicant-disease interaction with perchlorate that would constitute an added vulnerability and uncertainty consideration.

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4. Deriving a Distribution of Thyroid Hormone Levels from the BBDR Model Output

While the BBDR model can be calibrated to match specific percentiles of the population, the distributions in the underlying parameters required to *predict* the distribution of thyroid hormone levels have not been determined. Therefore, in order to predict the impact of perchlorate exposure on the population *distribution* of fT4 (i.e., on the population fraction of hypothyroxinemic individuals; those with fT4 below the reference range, with TSH in the normal range) it is necessary to first determine a distribution for fT4 plasma concentrations around the median values. This section describes the process of estimating these distributions.

4.1 Evaluation of Distributional Shape and Derivation of the Geometric Standard Deviation

Results from the literature review (see Section 5 and Section 6) suggested that it would be most useful to estimate distributions around the BBDR model output for 12, 13, and 16 weeks of gestation. Furthermore, this review suggested that it would be most useful to concentrate on fT4 rather than other thyroid hormones. To develop population distributions for fT4 serum concentrations around the BBDR-estimated median fT4 values, the fT4 data used to calibrate the BBDR model were evaluated (see Figure A-33 in Appendix A). Only one study provided distributional data for gestational week 13 fT4 (Männistö et al., 2011), and therefore, the studies were combined for weeks 12 and 13 in order to estimate distributional parameters that may be relevant for both gestational weeks. 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 evaluated for week 16, as Li et al. (2014) did not provide data for gestational week 16.

To evaluate the shape of the fT4 distribution, skewness was evaluated. With the exception of the Zhang et al. (2016) week 16 data, all of the examined study data demonstrated a positive skew (see Table 4), suggesting a lognormal distribution. To further confirm the assumption of a lognormal distribution, estimated 2.5th, 50th, and 97.5th percentiles were evaluated using the lognorm.inv and norm.inv functions in Excel, and overall the lognormal function demonstrated a better fit than a normal distribution. An example of the calculations used to determine the skewness of each dataset can be found in Table 4.

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Table 4. Distances between 2.5th and 50th Percentile, and 50th and 97.5th Percentile fT4, Demonstrating Skewness of Relevant Study Data

Study – Gestational Week	2.5th to 50th Percentile Distance	50th to 97.5th Percentile Distance	Skewness
Li et al. (2014) – Week 12	**3.94**	5.16	0.40
Männistö et al. (2011) – Week 12	**3.68**	5.94	0.68
Männistö et al. (2011) – Week 13	**3.25**	6.36	0.91
Zhang et al. (2016) – Week 12	**3.09**	3.56	0.21
Männistö et al. (2011) – Week 16	**3.58**	5.34	0.58
Zhang et al. (2016) – Week 16	3.03	**2.74**	-0.15

Bold results indicate shortest distance from actual 50th percentile and either actual 2.5th percentile or actual 97.5th percentile of study data.
Skewness was calculated by inputting 2.5th, 50th, and 97.5th percentiles of study data into the SKEW function in Excel.
fT4 values are measured in pmol/L.

After determining that the lognormal distribution was preferred to the normal distribution, summary geometric standard deviations (GSDs) were estimated using information from each relevant study. Two weighted GSDs were developed: a weighted GSD for weeks 12 and 13, and a second weighted GSD for week 16. To calculate these GSDs, the back-calculated[8] GSDs used to estimate 2.5th and 97.5th percentiles of fT4 were averaged, resulting in a single GSD from each study and week (grouping together week 12 and 13 into one week). Both estimated GSDs for each study and week are presented in Table 5 along with their averages.

Each average GSD was then weighted based on the number of study participants in the relevant gestational week from each study. This yielded a representative GSD for weeks 12 and 13, and a representative GSD for week 16, both based on the relevant data from each relevant study. The relevant sample sizes from each study and week are also presented in Table 5, along with the final weighted GSDs. The weighted GSDs were estimated to be 0.150 for weeks 12 and 13, and 0.134 for week 16. These GSDs were assumed to represent the median-iodine intake distribution, as this is what these studies were used for in model calibration.

[8] GSDs were back-calculated by performing an iterative process of inputting values for the GSD into the lognorm.inv Excel function, and revising the GSD based on the agreement of the function-predicted 2.5th/97.5th percentile and the actual 2.5th/97.5th percentile reported in each particular study, given the input of the natural logarithm of the 50th percentile of the study data as the geometric mean.

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Table 5. Estimated GSDs, Sample Sizes, and Summary Weighted GSDs Based on Data from Relevant Studies with fT4 Data from Gestational Weeks 12, 13, and 16

Study - Gestational Week	Estimated GSD to fit 2.5th Percentile	Estimated GSD to fit 97.5th Percentile	Average GSD	Sample Size	Weighted GSD Median Iodine Intake	Weighted GSD Low Iodine Intake
Weeks 12 and 13						
Li et al. (2014) – Week 12	0.15595	0.15120	0.15358	125	**0.150**	**0.138**
Männistö et al. (2011) – Week 12	0.14111	0.16800	0.15456	454		
Männistö et al. (2011) – Week 13	0.12487	0.18065	0.15276	325		
Zhang et al. (2016) – Week 12	0.11569	0.10718	0.11144	87		
Week 16						
Männistö et al. (2011) – Week 16	0.14290	0.15860	0.15075	111	**0.134**	**0.124**
Zhang et al. (2016) – Week 16	0.12990	0.09444	0.11217	85		

Given that these studies were used to calibrate the model for the median-iodine intake results, it was also necessary to calculate a GSD for the lower iodine intake. To do this, the coefficient of variation was assumed to remain constant between the median-iodine group and the low-iodine group. This is because the ratio of the distances between the 2.5th and the 50th percentile, and the 50th and the 97.5th percentile, appeared to remain mostly constant between studies whereas the standard deviation changed. Therefore, the GSD was decreased by the same percentage that the natural logarithm of the median fT4 level decreased when going from 170 µg/day to 75 µg/day iodine intake. For week 12, the BBDR model predicts a -7.9% change in the median natural log fT4 level from 170 to 75 µg/day iodine intake. Therefore, a 7.9% change in the GSD was calculated for the lower iodine intake at 12 GW, which resulted in an estimated GSD of 0.138. For week 13, the BBDR model predicted a -7.8% change in the median natural log fT4 level from 170 to 75 µg/day iodine intake and for week 16, a -7.7% change in the median natural log fT4 level from 170 to 75 µg/day iodine intake. The resulting GSDs used for each iodine level are described in Table 5.

4.2 Results of Estimating a Distribution around BBDR Median Output

With the calculated GSDs, it was then possible to estimate distributions of fT4 around any dose of perchlorate. This was done using the lognorm.inv function as described in Ginsberg et al. (2014). Table 6, Table 7, and Table 8 demonstrate fT4 distributions for various doses of perchlorate based on our calculated GSDs for gestational weeks 12, 13, and 16, respectively, for both median iodine intake and low iodine intake.

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Table 6. Summary of BBDR Model Results for fT4 for GW 12 at 75 and 170 µg/day Iodine Intake

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	7.95	8.33	8.80	10.67	13.65	14.31
1	7.95	8.33	8.80	10.66	13.64	14.31
2	7.94	8.33	8.79	10.66	13.64	14.30
3	7.94	8.32	8.79	10.65	13.63	14.29
4	7.94	8.32	8.79	10.65	13.63	14.29
5	7.93	8.32	8.78	10.64	13.62	14.28
10	7.91	8.30	8.76	10.62	13.59	14.24
Iodine Intake = 75 µg/day[b]						
0	6.75	7.05	7.41	8.85	11.11	11.60
1	6.70	6.99	7.35	8.78	11.02	11.51
2	6.65	6.94	7.30	8.71	10.94	11.42
3	6.60	6.89	7.24	8.65	10.86	11.34
4	6.55	6.84	7.19	8.59	10.78	11.26
5	6.51	6.79	7.14	8.53	10.71	11.18
10	6.31	6.59	6.93	8.27	10.38	10.84

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a lognormal distribution with a GSD = 0.150.
[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a lognormal distribution with a GSD = 0.138.

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Table 7. Summary of BBDR Model Results for fT4 for GW 13 at 75 and 170 µg/day Iodine Intake

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	7.93	8.32	8.78	10.64	13.62	14.28
1	7.93	8.31	8.78	10.64	13.62	14.27
2	7.92	8.31	8.77	10.63	13.61	14.27
3	7.92	8.30	8.77	10.63	13.60	14.26
4	7.92	8.30	8.77	10.62	13.60	14.25
5	7.91	8.30	8.76	10.62	13.59	14.25
10	7.89	8.27	8.74	10.59	13.55	14.21
Iodine Intake = 75 µg/day[b]						
0	6.74	7.04	7.41	8.84	11.10	11.59
1	6.69	6.99	7.35	8.77	11.01	11.50
2	6.64	6.94	7.29	8.71	10.93	11.41
3	6.59	6.88	7.24	8.64	10.85	11.33
4	6.54	6.84	7.19	8.58	10.77	11.25
5	6.50	6.79	7.14	8.52	10.70	11.18
10	6.30	6.58	6.92	8.27	10.38	10.84

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a lognormal distribution with a GSD = 0.150.
[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a lognormal distribution with a GSD = 0.138.

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Table 8. Summary of BBDR Model Results for fT4 for GW 16 at 75 and 170 µg/day Iodine Intake

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	7.88	8.22	8.63	10.25	12.77	13.32
1	7.87	8.21	8.62	10.24	12.76	13.31
2	7.87	8.21	8.62	10.23	12.76	13.31
3	7.86	8.20	8.61	10.23	12.75	13.30
4	7.86	8.20	8.61	10.22	12.74	13.29
5	7.85	8.19	8.60	10.21	12.73	13.28
10	7.83	8.16	8.57	10.18	12.69	13.23
Iodine Intake = 75 µg/day[b]						
0	6.72	6.98	7.30	8.56	10.49	10.90
1	6.67	6.93	7.25	8.49	10.41	10.82
2	6.62	6.88	7.20	8.43	10.33	10.75
3	6.57	6.83	7.15	8.37	10.26	10.67
4	6.53	6.79	7.10	8.32	10.19	10.60
5	6.49	6.74	7.05	8.27	10.13	10.53
10	6.30	6.55	6.85	8.03	9.83	10.23

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a lognormal distribution with a GSD = 0.134.
[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a lognormal distribution with a GSD = 0.124.

4.3 Limitations and Uncertainties of Method

The lognormal distribution is assumed to be the proper description of the distribution of fT4 given that it exhibits a better fit to empirical distributions of fT4 than the normal distribution. It is possible that a different positively skewed distributional form may describe the variability in fT4 better than the lognormal distribution. Additionally, as only two studies used to calibrate the model for fT4 provided distributional data from week 16, it is unclear whether the lognormal distribution is indeed a better distributional shape than the normal distribution. As presented in Table 4, it is clear that the Männistö et al. (2011) data suggest a lognormal distribution, while the Zhang et al. (2016) data point to the normal distribution as the preferred distributional shape. In this instance, to remain consistent with the analysis for weeks 12 and 13, EPA chose to use the lognormal distribution to describe the fT4 data.

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5. Connecting Alterations in Thyroid Hormone Levels to Alterations in Neurodevelopment: Identification of Studies for Further Analysis

This section addresses the SAB recommendation to "identify literature and conduct analyses to support the model outputs for the downstream steps" (SAB, 2013, pp. 27-28) from the BBDR's predicted changes in thyroid hormones. Specifically, this section presents the process by which literature was identified to complete the linkage between altered maternal T4 and fT4 (as predicted by the BBDR model) and adverse neurodevelopmental effects in offspring. Section 5.1 presents the process used to identify the literature to support this approach. Sections 5.2 and 5.3 describe the literature search approach and results of the process used to identify relevant studies that can link the predictions of changes in fT4 from the BBDR model to incremental changes in neurodevelopment. Section 5.4 presents results from the literature that are used to support an alternative proposed approach presented in Section 7: evaluating a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate.

5.1 Searching the Published Literature

The available data for the second stage of the analysis comes from epidemiological studies that evaluated maternal thyroid hormone levels in 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 epidemiological studies that examined thyroid hormone levels and neurodevelopmental outcomes.

EPA conducted the literature searches in PubMed and Google Scholar focusing on epidemiologic studies that explicitly evaluated the association between maternal thyroid hormone T4 or fT4 levels and offspring neurodevelopment. A protocol was developed to identify and evaluate the studies located. *A priori* study attributes were defined (see Section 5.2.3) and studies were categorized based on whether the analysis was based on a categorical or a continuous measure of thyroid hormones as they related to neurodevelopment. Search strings and categories are presented in Table 9. As depicted in this table, the endpoints included neurodevelopmental measures, autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD). These categories were chosen as outcomes associated with alterations in thyroid hormone levels based on the 2013 SAB recommendations, CalEPA's *Public Health Goal for Perchlorate* (CalEPA, 2011) and the National Research Council's *Health Implications for Perchlorate (NRC, 2005).*

Searches were restricted to studies published from 2000 to limit the results to the most recent science. Limiting studies to the past 17 years was supported by Pop et al. (1999) (this study was identified by SAB, 2013), who noted there were no studies evaluating the relationship between maternal thyroid hormone levels and infant neurodevelopment from iodine-sufficient populations prior to 1999. In addition, the SAB document (2013) was reviewed to confirm that the literature search captured all of the studies cited as potential references that evaluate the relationship between thyroid hormone and neurodevelopment (e.g., pages 10, 15, and 28 of SAB, 2013), including some that were published prior to 2000. Titles and abstracts of all studies were reviewed to determine if the study had pertinent

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information relating thyroid hormone levels, particularly T4 or fT4, and adverse neurodevelopmental outcomes.

Reviewing the Google Scholar and PubMed literature searches resulted in the identification of 49 studies that assessed the relationship between maternal thyroid hormone levels and neurodevelopmental outcomes in the offspring. The review of the SAB document identified six additional papers[9] to evaluate, resulting in a total of 55 studies that pertained to altered maternal thyroid hormone levels and offspring neurodevelopment.

Table 9. Summary of Search Strings Conducted

Search Category	Search Strings[a]
Endpoint: Neurodevelopment	• Neurodevelopment AND hypothyroxinemia[b] • "Neurodevelopmental effects" AND hypothyroxinemia[b] • Hypothyroxinemia AND behavior • Hypothyroxinemia AND behavior AND infant • Hypothyroxinemia AND thyroxine AND behavior AND infant • (Thyroxine OR T4 OR hypothyroxinemia) AND (neurodevelopment OR "mental ability" OR intelligence OR cognition OR cognitive OR motor OR language)
Endpoint: Attention Deficit/ Hyperactivity Disorder	• "Maternal hypothyroxinemia" AND thyroxine AND ADHD AND infant
Endpoint: Autism	• Hypothyroxinemia AND autism[b] • Hypothyroxinemia AND thyroxine AND autism AND infant

[a] Searches were restricted to studies published from 2000 to January 2017.
[b] This search string resulted in more articles than EPA could reasonably evaluate. Therefore, the search was constrained so that databases searched for those terms only in the title.

5.2 Approach to Locate Epidemiological Studies that Evaluated Maternal Thyroid Hormone Levels in Early Pregnancy and Neurodevelopmental Outcomes

To identify studies linking maternal T4 or fT4 to offspring neurodevelopment (Step 2 in Figure 1), EPA assessed each of the 55 studies identified using a three-step approach. First, studies were identified that were not compatible with BBDR model results (see 5.2.1). Studies were then categorized depending on whether the analysis was based on a categorical or a continuous measure of thyroid hormones as they related to neurodevelopment (see 5.2.2). Those studies were then evaluated based on pre-established attributes and relevant and necessary data for additional analyses (see 5.2.3).

Each step is described below.

[9] Haddow et al., 1999; Man, Brown and Serunian, 1991; Pharoah, Connolly, Ekins, and Harding, 1984; Pop et al., 1999; Velasco et al., 2009; Willoughby, 2011.

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5.2.1 Step 1. Identify Studies That are Not Compatible with BBDR Model Results

First, studies were identified that are not compatible with BBDR model results for MCLG development. Specifically, studies were identified with the following features:

- The study design is not directly compatible with the BBDR model results. For example, if the study only evaluated the impact of neonatal thyroid hormones (i.e., 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 for MCLG development. 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.
- 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.[10] The neurodevelopmental outcomes could be measured at any life stage.

Any studies identified in this step were categorized as Group 3.

5.2.2 Step 2. Categorize the Remaining Studies

The remaining studies were evaluated based on the analysis approach presented in the study. Studies were categorized that allow for the estimation of a given change in thyroid hormones that is responsible for a specified change in a neurodevelopmental outcome. Specifically:

- Studies that present any analyses based on a continuous measure of maternal thyroid hormone levels and subsequent offspring neurodevelopmental outcomes were placed into Group 1. These studies present data to inform an analysis that allows for an understanding of the impact of incremental changes in thyroid hormones and subsequent neurodevelopmental impacts.
- Studies that present analyses based only on categorical analyses of thyroid hormones (e.g., yes/no hypothyroxinemic) and subsequent neurodevelopmental were placed into Group 2.

5.2.3 Step 3. Identify Group 1 Studies that Present Data to Inform a Dose-Response Relationship

After identifying all studies that present analyses based on a continuous measure of thyroid hormone levels, EPA reviewed the Group 1 studies to identify those for which additional quantitative analysis could be conducted. 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. These studies were further characterized and summarized. The specific attributes characterized and the value of the type of data supplied in the study are described below:

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[10] Although the EPA model provides estimates for women through the 16th gestational week, the gestational week of thyroid hormone data was not a factor in categorizing a study in group 3. Additional evaluation was conducted to determine the feasibility of linking the study findings with BBDR model output.

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- *The population for which the dose-response information is available.* That is, if the analyses presented in each paper are based on the full spectrum of thyroid hormone levels or if the analysis is only based on hypothyroxinemic thyroid hormone levels. The SAB stated that fetuses of hypothyroxinemic women may be a potentially sensitive life stage (SAB, 2013).
- *The endpoint evaluated.* There are numerous indices by which to assess neurodevelopmental impacts. Some evaluate a single attribute of neurodevelopment (e.g., language delay), whereas others evaluate a broader set of attributes. For example, the Bayley Scales of Infant Development (BSID) evaluate a range of abilities via several indices that are summed to a single score representing psychomotor or mental development.[11]
- *Iodine intake data for the study population.* Iodine intake status may impact neurodevelopmental outcomes and the BBDR model presents dose-response information by iodine intake level. 24-hour iodine intake information is more complete than spot sample urinary iodine intake data.
- *The method of thyroid hormone sampling.* Repeated thyroid hormone measurements give a more complete picture as to how alterations in thyroid homeostasis impact neurodevelopment throughout gestation. Given that perchlorate exposure likely does not occur in just one phase of gestation or early infancy, having a more comprehensive evaluation of the impact of thyroid hormone levels on neurodevelopment may provide a better concept of how suppressed thyroid hormone levels impact neurodevelopment throughout pregnancy or early infancy.
- *The timing of the thyroid hormone measurement.* In regard to maternal thyroid hormone levels, fT4 in early pregnancy (i.e., prior to fetal thyroid hormone development, which occurs between gestational weeks 12 and 16) is believed to be most important in regard to neurodevelopmental outcomes (Morreale de Escobar, 2001; Morreale de Escobar et al., 2004).
- *The size of the study population.* A larger cohort may have more power to detect a subtle difference in an outcome compared to a smaller one. Additionally, a larger study may be more easily extrapolated compared to a smaller study. However, smaller studies have benefits as well. For example, some of the standard neurodevelopmental evaluations require one-on-one assessments, which may not be feasible in cohorts with thousands of individuals. Further, a small study that does detect an association is notable given the lack of power that is associated with a small sample size.

For the purposes of this document, EPA is not selecting a key paper (or papers) on which to rely to inform the derivation of an MCLG for perchlorate. Instead, this report presents evaluations of all identified papers with relevant and necessary data and approaches for how they may inform the derivation of an MCLG.

5.3 Results of Evaluation to Identify Studies That Directly Relate Thyroid Hormone Levels with Neurodevelopment

As presented in Figure 6, the literature review identified 55 studies that link thyroid hormone levels to neurodevelopmental effects. These studies were divided into three groups to facilitate evaluation:

[11] This statement pertains to the BSID Version I and Version II.

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- Group 1: Studies that may be able to quantitatively describe a relationship between incremental alterations in maternal thyroid hormone levels and alterations in offspring neurodevelopment.
- Group 2: Studies that do not have data from which to derive a quantitative relationship between maternal thyroid hormones and offspring neurodevelopment, but instead present only categorical analysis with thyroid hormones below and above a defined cut point and adverse neurodevelopmental outcomes.
- Group 3: Studies that present an analysis that is not directly compatible with BBDR output. For example, if the study only had data on TSH or only measured thyroid hormone levels in children, it would not inform use of the BBDR output.

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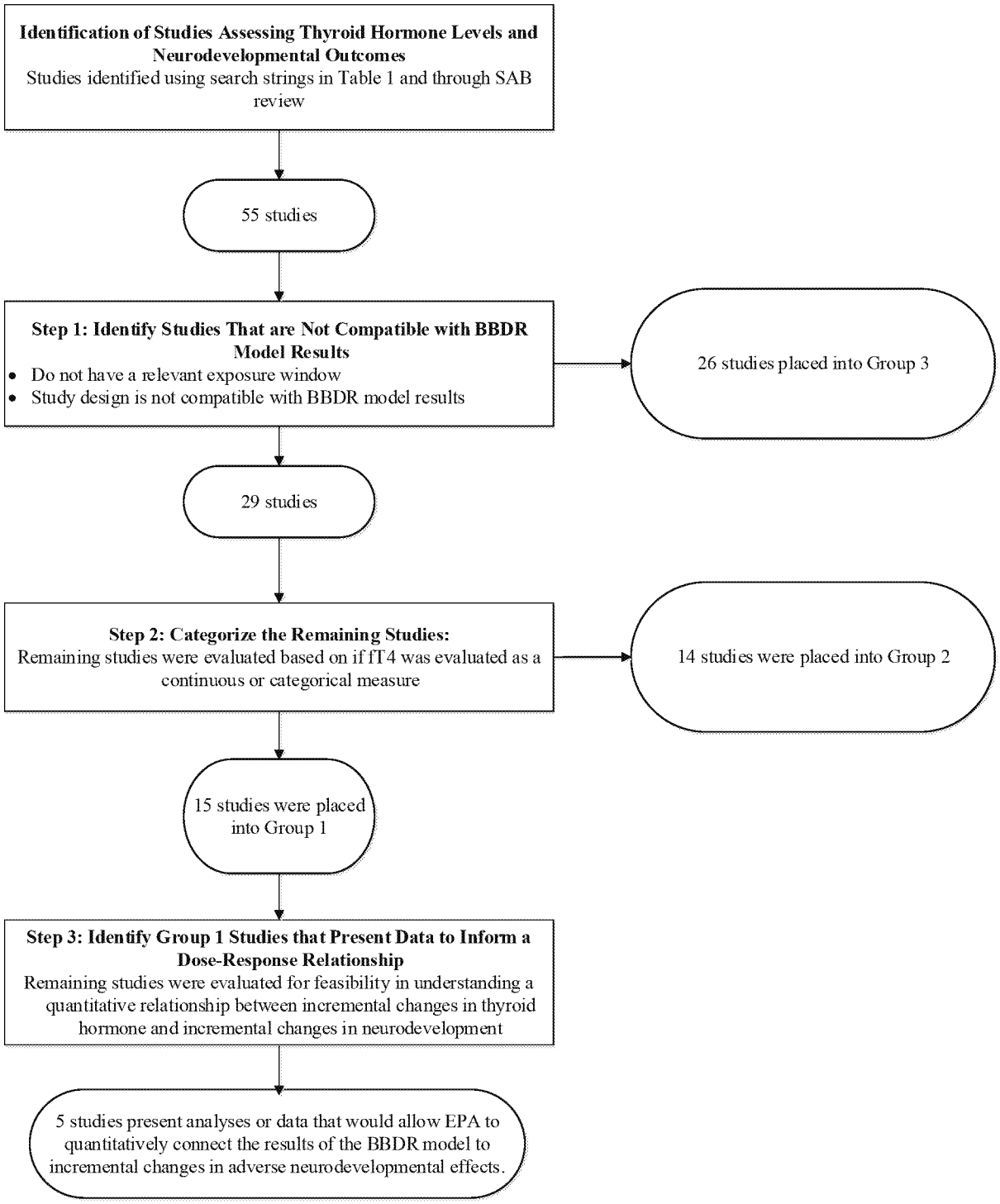
Figure 6. Overview of Process and Results to Assess Studies Relating Thyroid Hormone Levels to Neurodevelopmental Outcomes



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Following the process outlined above, 15 studies were ultimately identified as Group 1 and subsequently evaluated to determine if relevant and necessary data was available for further analysis. Five of the Group 1 studies conducted analyses or presented data that would allow EPA to quantitatively connect the results of the BBDR model to incremental changes in adverse neurodevelopmental effects. The following sections provide more detail about the process involved in each step of the evaluation and the results.

5.3.1 Results of Step 1

Out of the 55 papers identified in the literature review, EPA identified 26 that are not compatible with BBDR model results. These Group 3 studies are listed in Table 10 along with the reason the study is not compatible with BBDR model results. Table 10 also lists the life stage of thyroid hormone measurement to aid in comparison across studies. Short summaries of each study in Group 3 are presented in Appendix D.

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Table 10. List of Studies Identified in Step 1 and Categorized as Group 3 with Rationale for Categorization

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Cusick and Georgieff (2016) *The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days"*	The study design is not directly relevant to the BBDR model results. This is a review paper that provides a narrative discussion and does not provide quantitative information to measure neurodevelopmental outcomes.	n/a
Dosiou and Medici (2017) *Management of Endocrine Disease: Isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns*	The study design is not directly relevant to the BBDR model results. This is a review paper that does not provide quantitative information on the relationship between fT4 and outcomes.	Pregnant woman
Furnica et al. (2015) *Update on a new controversy in endocrinology: isolated maternal hypothyroxinemia*	The study design is not directly relevant to the BBDR model results. This is a review paper that does not provide quantitative information on the relationship between fT4 and outcomes.	Pregnant woman
Gutleb et al. (2016) *Impact of Endocrine Disruptors on the Thyroid Hormone System*	The study design is not directly relevant to the BBDR model results. This paper reviewed the effects that endocrine disruptors may have on the thyroid and did not evaluate the impact of thyroid hormones on neurodevelopment in offspring.	n/a
Haddow et al. (1999) *Maternal Thyroid Deficiency During Pregnancy and Subsequent Neuropsychological Development of the Child*	The study design is not directly relevant to the BBDR model results. The study only evaluated TSH and did not include data on T4 or fT4.	Pregnant woman
Hamza, Hewedi, and Sallam (2013) *Iodine Deficiency in Egyptian Autistic Children and Their Mothers: Relation to Disease Severity*	Did not have a population with an exposure that overlaps with the outputs for the BBDR model. The study measured thyroid hormones in autistic children.	Child
Hollanders et al. (2015) *No Association Between Transient Hypothyroxinemia of Prematurity and Neurodevelopmental Outcome in Young Adulthood*	The study design is not directly relevant to the BBDR model results. The study assesses the impact of transient hypothyroxinemia of prematurity in pre-term or very low birthweight infants.	Neonate, child
Hollanders et al. (2016) *Transient hypothyroxinemia of prematurity and problem behavior in young adulthood*	The study design is not directly relevant to the BBDR model results. The study assesses the impact of transient hypothyroxinemia of prematurity in pre-term infants or very low birthweight infants.	Neonate, child
Hoshiko, Grether, Windham, Smith, and Fessel (2011) *Are Thyroid Hormone Concentrations at Birth Associated with Subsequent Autism Diagnosis?*	Did not have a population with an exposure that overlaps with the outputs for the BBDR model. Thyroid hormone samples were measured in neonates within 24 hours of birth.	Neonate

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Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Korzeniewski et al. (2013) *Association Between Transient Hypothyroxinemia of Prematurity and Adult Autism Spectrum Disorder in a Low-Birthweight Cohort: An Exploratory Study*	The study design is not directly relevant to the BBDR model results. The study only examined low-birthweight/pre-term infants.	Neonate
Leung (2015) *Maternal Hypothyroxinemia in the Late First Trimester May Affect Offspring Math Performance At 5 Years of Age*	The study design is not directly relevant to the BBDR model results. This is a narrative discussion of Noten et al. (2015).	Pregnant woman
Lyall et al. (2016) *Neonatal thyroid hormone levels in association with autism spectrum disorder*	Did 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. The study only measured thyroid hormones (T4 and TSH) in bloodspots of newborn infants.	Neonate
Man, Brown, and Serunian (1991) *Maternal Hypothyroxinemia: Psychoneurological Deficits of Progeny*	The study design is not directly relevant to the BBDR model results. The study measured butanol-extractable iodine and did not include data on T4 or fT4.	Pregnant woman
Min et al. (2016) *Maternal Hypothyroxinemia-Induced Neurodevelopmental Impairments in the Progeny*	The study design is not directly relevant to the BBDR model results. This is a review paper that does not provide quantitative information to measure neurodevelopmental outcomes.	Pregnant woman
Pearce (2015a) *Maternal Hypothyroxinemia in Pregnancy Is Associated with Increased Risk for ADHD Symptoms in Children*	The study design is not directly relevant to the BBDR model results. This is a narrative discussion of Modesto et al. (2015).	Pregnant woman
Pérez-Lobato et al. (2014) *Thyroid Status and Its Association with Cognitive Functioning in Healthy Boys at 10 Years of Age*	Did not have a population with an exposure that overlaps with the outputs for the BBDR model. Thyroid hormones were measured in children (mean age was 9.8 years).	Child
Pharoah, Connolly, Ekins, and Harding (1984) *Maternal Thyroid Hormone Levels in Pregnancy and the Subsequent Cognitive and Motor Performance of the Children*	The study design is not directly relevant to the BBDR model results. The study population was severely iodine-deficient.	Pregnant woman
Scratch et al. (2014) *Free Thyroxine Levels After Very Preterm Birth and Neurodevelopmental Outcomes at Age 7 Years*	The study design is not directly relevant to the BBDR model results. The study only examined very pre-term births.	Neonate

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Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Soldin et al. (2002) *Newborn Thyroxine Levels and Childhood ADHD*	Did not have a population with an exposure window that overlaps with outputs for the BBDR model. The study only measured thyroid hormone in infants.	Neonate
Soldin, Lai, Lamm, and Mosee (2003) *Lack of a Relation Between Human Neonatal Thyroxine and Pediatric Neurobehavioral Disorders*	Did not have a population with an exposure window that overlaps with outputs for the BBDR model. The study only measured thyroid hormone in infants.	Neonate
Tiemeier and Korevaar (2016) *A New Modifiable Risk Factor for Schizophrenia?*	The study design is not directly relevant to the BBDR model results. This is a commentary article that does not provide quantitative information to measure neurodevelopmental outcomes.	n/a
F. Williams et al. (2012) *Mild Maternal Thyroid Dysfunction at Delivery of Infants Born ≤34 Weeks and Neurodevelopmental Outcome at 5.5 Years*	The study design is not directly relevant to the BBDR model results. This study evaluated the effect of maternal thyroid dysfunction on pre-term infants.	Neonate, pregnant woman
F. Williams et al. (2013) *Maternal and Umbilical Cord Levels of T_4, fT4, TSH, TPO Ab, and TgAb in Terms Infants and Neurodevelopmental Outcome at 5.5 Years*	Did not have a population with an exposure that overlaps with the outputs for the BBDR model. Maternal fT4 was not evaluated in association with the neurodevelopmental outcome.	Fetus, pregnant woman
Willoughby (2011) *Effects of Early Thyroid Hormone Deficiency on Autobiographical Memory and Hippocampal Structure During Late Childhood and Early Adolescence*	The study design is not directly relevant to the BBDR model results. The only results for T4 are related to cases of congenital hypothyroidism.	Child, neonate, pregnant woman
Willoughby, McAndrews, and Rovet (2014) *Effects of Maternal Hypothyroidism on Offspring Hippocampus and Memory*	The study design is not directly relevant to the BBDR model results. The results of the study pertain to the offspring of hypothyroid women.	Pregnant woman
Wong et al. (2016) *Developmental Assessments in Preterm Children: A Meta-analysis*	The study design and is not directly relevant to the BBDR model results. This study evaluated the risk of pre-term birth from thyroid disease.	n/a

[a] Pregnant woman: thyroid hormone measurement taken anytime during pregnancy; Fetus: thyroid hormone levels were measured from cord blood at birth. Neonate: thyroid hormone levels were measured from a source other than cord blood between birth and 28 days of age. Child: thyroid hormone levels were measured after 1 year of age.

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5.3.2 Results of Step 2

After identifying 26 studies to categorize as Group 3 in Step 1, 29 studies remained for categorization in Step 2. From each study it was determined whether or not an analysis was presented that was based on a continuous measure of thyroid hormones. Fourteen studies were placed into Group 2 given that they only presented categorical analyses, and 15 were placed into Group 1 because they presented a continuous regression analysis. Group 1 studies may also have categorical results, but they were categorized based on the presence of any analysis based on a continuous measure of thyroid hormone levels. Summaries of the studies in each group are presented in subsequent sections.

Summary of Studies in Group 2

Of the 29 studies evaluated in Step 2, 14 studies provide categorical data that assist in understanding the implications of altered maternal thyroid hormone levels and potential adverse neurodevelopmental outcomes in their offspring. However, these studies do not present data to inform an analysis that allows for an understanding of the impact of incremental changes in thyroid hormones and subsequent neurodevelopmental impacts. These studies are summarized in Table 11.

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Table 11. Overview of Studies Categorized as Group 2

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Berbel et al. (2009) *Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation*	43 Spanish mother-child pairs in 3 groups based on fT4 level and timing of iodine supplementation[c]	fT4 < 10th percentile (< 10.6)	A delay of 6–10 weeks in iodine supplementation of hypothyroxinemic mothers at the beginning of gestation increased the risk of neurodevelopmental delay.	Pregnant woman
Costeira et al. (2011) *Psychomotor Development of Children from an Iodine-Deficient Region*	86 Portuguese mother-child pairs from iodine-deficient region (n_{cases} = 8)	fT4 < 10th percentile (<9.0 pg/mL or < 11.6)	Children born to mothers with low fT4 had increased odds of mild-to-severe delay in psychomotor development compared to children born to mothers with fT4 within the population reference range. Neonatal thyroid status did not influence development.	Neonate, pregnant woman
Craig et al. (2012) *Mid-Gestational Maternal Free Thyroxine Concentration and Offspring Neurocognitive Development at Age Two Years*	198 mother-child pairs in Maine, matched on fT4 levels (case: 3rd percentile or less control: 10th-90th percentile) (n_{cases} = 98)	fT4 ≤ 3rd percentile (< 11.8)	Unadjusted scores on the Bayley Scale III were lower at 2 years of age in children born to mothers with low fT4 in the second trimester (17 gestational weeks (GW)) as compared to children born to mothers with fT4 levels within the population reference range (10th to 90th percentile, or 12.9 to 17.2 pmol/L). After adjustment for confounding variables, differences were diminished, but 10th percentile fT4 levels were still associated with lower scores on the Bayley Scale.	Pregnant woman
Fan and Wu (2016) *The Impact of Thyroid Abnormalities during Pregnancy on Subsequent Neuropsychological Development of the Offspring: A Meta-Analysis*	4,449 mother-child pairs identified through multiple studies. (n_{cases} = 310)[d]	Multiple studies evaluated, no set definition	Children born to hypothyroxinemic mothers had mean intelligence and motor scores 5.7 and 4.2 points lower than non-hypothyroxinemic mothers, respectively.	Pregnant woman

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Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Ghassabian, Henrichs, and Tiemeier (2014) *Impact of Mild Thyroid Hormone Deficiency in Pregnancy on Cognitive Function in Children: Lessons from the Generation R Study*	3,903 Dutch mother-child pairs (n_{cases} = 129)	Severe: fT4 < 5th or 10th percentile of sample (exact value not defined)	This paper reviews the literature from the Generation R cohort and presents novel results related to ADHD and maternal hypothyroxinemia. In summary, prenatal exposure to maternal hypothyroxinemia increased the risk of ADHD, expressive language delay, and nonverbal cognitive delay in preschool-age children.	Fetus, Pregnant woman
Grau et al. (2015) *Normal Intellectual Development in Children Born from Women with Hypothyroxinemia During Their Pregnancy*	455 Spanish mother-child pairs at age 1 assessment 289 Spanish mother-child pairs at age 6-8 assessment (1 yr 1st trimester cases = 47; 1 yr 2nd trimester cases = 42; 6-8 yr 1st trimester cases = 33; 6-8 yr 2nd trimester cases = 28)	fT4 < 10th percentile (< 13.7) (first trimester) fT4 < 10th percentile (11.5 pmol/L) (second trimester)	Children of mothers with hypothyroxinemia in the first and second trimester from an iodine-sufficient area did not have adverse neurodevelopmental outcomes (assessed at age 1 with the Brunet-Lezine scale and age 6 to 8 with the Wechsler Intelligence Scale for Children) associated with levels of fT4.	Pregnant woman
Júlvez et al. (2013) *Thyroxine Levels During Pregnancy in Healthy Women and Early Child Neurodevelopment*	1,643 Spanish mother-child pairs (n_{cases} = 164)	Low fT4 (less than 10th (8.89), 5th (8.39) or 2.5th (8.10) percentile)	Children born to mothers with lower fT4 (<10th percentile (<8.89 pmol/L)) show a decrease in Bayley's Score compared to children born to mothers with fT4 > 10th percentile.	Pregnant woman

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Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Kooistra, Crawford, van Baar, Brouwers, and Pop (2006) *Neonatal Effects of Maternal Hypothyroxinemia During Early Pregnancy*	204 Dutch mother-child pairs (n_{cases} = 108)	fT4 < 10th percentile (< 10.4)	Infants of women with hypothyroxinemia at 12 GW had a lower neonatal Behavioral Assessment Scale orientation index compared with infants of non-hypothyroxinemic women. Neonatal thyroid hormone levels were not assessed in regard to neurodevelopment.	Neonate, pregnant woman
Li et al. (2010) *Abnormalities of Maternal Thyroid Function During Pregnancy Affect Neuropsychological Development of Their Children at 25-30 Months*	57 Chinese mother-child pairs (n_{cases} = 19)	fT4 < 5th percentile (< 11.9)	Children of hypothyroxinemic women had significantly lower mean mental and psychomotor development (Bayley's) scores at 25-30 months compared to children of non-hypothyroxinemic women.	Pregnant woman
Päkkilä et al. (2014) *The Impact of Gestational Thyroid Hormone Concentration on ADHD Symptoms of the Child*	5,131 Finnish mother-child pairs (n_{cases} = 66)	fT4 < 11.4 in the first trimester fT4 < 11.1 in the second trimester	Maternal hypothyroxinemia was not significantly associated with teacher ratings of ADHD symptoms in children at 8 years of age.	Pregnant woman
Päkkilä et al. (2015) *Maternal and Child's Thyroid Function and Child's Intellect and Scholastic Performance*	5,295 Finnish mother-child pairs with sufficient maternal serum samples (n_{cases} = 67)	fT4 < 11.4 in the first trimester fT4 < 11.1 in the second trimester [e]	Female offspring of mothers with subclinical hypothyroidism had more self-evaluated difficulties in mathematics than did females of mothers with thyroid function within the population reference range. Male offspring of hypothyroxinemic mothers repeated a school class more often than did males of mothers with normal thyroid function. Male offspring of hypothyroxinemic mothers also had a higher odds of having difficulties in Finnish and/or math.	Pregnant woman, child
Suárez-Rodríguez, Julián, and Aguilar (2012) *Hypothyroxinemia During Pregnancy: The Effect on Neurodevelopment in the Child*	70 Spanish mother-child pairs (n_{cases} = 37)	fT4 < 10th percentile (< 9.5)	Hypothyroxinemia was associated with lower scores on McCarthy Scales of Children's Abilities psychomotor developmental scales in children 38 and 60 months of age.	Pregnant woman

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Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
van Mil et al. (2012) *Maternal Hypothyroxinemia During Pregnancy and Growth of the Fetal and Infant Head*	2,621 Dutch mother-child pairs (n_{cases} = 476)	fT4 < 10th percentile (11.82)	Maternal hypothyroxinemia was associated with an increase in fetal head and infant head size. In addition, maternal hypothyroxinemia was associated with a statistically significant increased risk of cognitive delay.	Pregnant woman
Wang et al. (2016) *Maternal Thyroxine Levels During Pregnancy and Outcomes of Cognitive Development in Children*	8,273 mother-child pairs (n_{cases} = 702)[f]	Multiple studies evaluated, no set definition	Meta-analysis showed low maternal fT4 level was significantly associated with increase in risk of delayed cognitive development in offspring.	Pregnant woman

[a] Some studies did not explicitly define hypothyroxinemia, and instead examined the impact of altered thyroid hormone levels below a defined percentile cut point and of altered neurodevelopment. For the purposes of this review, these percentile cut points are considered to be analogous to a definition for hypothyroxinemia.
[b] Pregnant woman: thyroid hormone measurement taken anytime during pregnancy. Fetus: thyroid hormone levels were measured from cord blood at birth. Neonate: thyroid hormone levels were measured from a source other than cord blood between birth and 28 days of age. Child: thyroid hormone levels were measured after 1 year of age.
[c] **Group 1:** fT4> 20th percentile at 4-6 gestational weeks and term, supplemented with 200 µg/day potassium iodine through term and lactation. Neurocognitive evaluation was done on children with mothers fT4>20th percentile at 4-6 weeks and at term. (n=13) **Group 2:** mildly hypothyroxinemic at 12-14 gestational weeks, supplemented with 200 µg/day potassium iodine through term and lactation. Neurocognitive evaluation done on children with maternal fT4 <10th percentile at 12-14 weeks and fT4>20th percentile at term (n=12) **Group 3:** enrolled at full term at which time they were supplemented with 200 µg/day potassium iodine throughout lactation. Neurocognitive evaluations done on children born to mother that had fT4<10th percentile at term. (n=18)
[d] The number of cases of hypothyroxinemia included in the Fan and Wu (2016) meta-analysis are summed from Table 1 of the paper. All case used in the pooled analysis, including subclinical hypothyroidism, sum to 397 women.
[e] Päkkilä et al. (2015) define hypothyroxinemia as "TSH within reference intervals with low fT4 concentrations" (p. 1365), but low fT4 is not defined. The lower range of the reference interval is 11.4 pmol/L for fT4 for the first trimester, and 11.09 pmol/L is the lower bound of the reference interval for the second trimester. These are assumed to be the cut points used to define low fT4.
[f] The number of cases with hypothyroxinemia was determined from Table 1 of the paper and deriving values from within individual studies if the number of cases was not indicated.

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Of the 14 studies in Table 11, 13 evaluated maternal hypothyroxinemia (or fT4 level) and neurocognitive outcomes in the offspring. 11 of these 13 studies provide general support for an inverse relationship between fT4 levels and neurodevelopment (Costeira et al., 2011; Craig et al., 2012; Fan and Wu, 2016; Ghassabian, Henrichs, and Tiemeier, 2014; Júlvez et al., 2013; Kooistra et al., 2006; Li et al., 2010; Päkkilä, 2015; Suárez-Rodríguez et al., 2012; van Mil et al., 2012; Wang et al., 2016). Specifically, five of the studies identified found an increased risk of a lower IQ in offspring due to low maternal fT4 during pregnancy (often defined as hypothyroxinemia) (Craig et al., 2012; Fan and Wu, 2016; Júlvez et al., 2013; Li et al., 2010; Suárez-Rodríguez et al., 2012). Of the studies that looked at neurodevelopmental outcomes beyond IQ and maternal hypothyroxinemia, the majority found an association (Costeira et al., 2011; Ghassabian, Henrichs, and Tiemeier, 2014; Kooistra et al., 2006; Päkkilä, 2015; van Mil et al., 2012; Wang et al., 2016). Additionally, Berbel et al., (2009) found that delayed iodine supplementation in hypothyroxinemic women from the beginning of gestation to later pregnancy stages increased the risk of neurodevelopmental delay in offspring. Another study found an association between maternal TSH and a measure of neurodevelopment in the offspring, but the same association was not found with maternal T4 or fT4 (Päkkilä et al., 2014).

While most of the available studies found adverse neurodevelopmental outcomes in the offspring of mothers with hypothyroxinemia, Grau et al. (2015) did not find this association. Grau et al. (2015) evaluated the relationship between maternal TSH, fT4, and fT3 measured in the first and second trimester with children's performance on the Brunet-Lezine[12] scale (at 1 year) and using the WISC-IV (i.e., IQ; at 6-8 years). To do their analysis they compared children born to hypothyroxinemic women (defined as fT4 < 10th percentile; 13.7 pmol/L for the first trimester; 11.5 pmol/L for the second trimester) to children born to euthyroid mothers with urinary iodide greater than 150 µg/L. At 1 year of age they found that the children born to hypothyroxinemic mothers scored lower on almost all of the scales assessed by the Brunet-Lezine scale (e.g., postural control, coordination/oculomotor, sociability), but the differences were small and not statistically significant. When assessing IQ, children born to hypothyroxinemic women actually performed better on most scales, but the differences again were small and not statistically significant. The results seen between the thyroid hormone measurements and neurodevelopmental outcomes in Grau et al. (2015) may be due to the high thyroid hormone levels of the women in this population, resulting in a high hypothyroxinemic cut point of 13.7 pmol/L. The authors also suggest that this population is likely from an iodine-sufficient area (hence the high fT4 levels) and is therefore less susceptible to alterations in maternal fT4.

Brief descriptions of all studies are presented in Appendix E.

[12] Developmental test that measures motor and mental development of children aged 2-30 months.

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Summary of Group 1 Studies

After categorizing 14 studies in Group 2, 15 remained to be categorized as Group 1. EPA focused on this set of fifteen studies due to the presence of an analysis which evaluated maternal fT4 as a continuous variable, as it related to offspring neurodevelopment. Group 1 includes studies that found statistically significant changes and those that did not. In many but not all of these studies the general results, though not statistically significant, were consistent with the studies used for further quantitative analyses by EPA. EPA presents and characterizes all of the Group 1 studies below.

Studies categorized in Group 1 present data that may allow for the extraction of a function relating a continuous measure of thyroid hormone levels to some measure of neurodevelopment. In combination with the BBDR model, this function may be used to identify the dose of perchlorate associated with a defined change in neurodevelopment. Several of the studies in this group did not include an estimated regression function, but instead presented a scatterplot that depicts a regression or correlation analysis.[13] The graphical data presented in these studies was digitized to allow for the estimation of a function. The papers categorized as Group 1 are summarized in Table 22 in Section 5.3.3, including findings related to the continuous relationship presented in the paper and information necessary to evaluate the papers as outlined above in Step 3. Many of these papers present regression analyses on more than one endpoint or age group. The majority of the continuous relationships presented pertain to the entire range of maternal fT4 and are not specific to just the offspring of hypothyroxinemic mothers. However, many of the Group 1 studies also present a categorical analysis comparing neurodevelopmental outcomes in the offspring of hypothyroxinemic and non-hypothyroxinemic mothers, this is discussed further in Section 5.4.

Detailed Summary of Chevrier et al. (2011)

Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age

Chevrier et al. (2011) examined the relationship between thyroid hormone levels during pregnancy and child neurodevelopment outcomes from 6 months to 5 years of age. Participants were recruited from a birth cohort study in the Salinas Valley, CA, and were primarily low-income Latina women. Maternal fT4, TSH, and total T4 levels were measured at the end of the second trimester, at a mean GW of 26.9. TPO Abs were not measured. Children were assessed using the Bayley Scales of Infant Development at 6, 12, and 24 months and the Preschool Language Scale at age 6 months and 12 months. The BSID provides two main indices for assessing neurodevelopment in children: the Mental Development Index and the Psychomotor Development Index. The MDI assesses cognitive and language development using items related to sensory perception, knowledge, memory, problem solving, and early language. The PDI evaluates fine and gross motor skills such as body control, coordination, and manipulation. At 5 years, children completed the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) to determine performance IQ, as well as a series of other scales to assess language development, memory, attention, and motor skills. The WPPSI performance IQ is a measure of reasoning, spatial processing, and visual-motor skills. Attention skills were additionally

[13] The authors of each of these studies were contacted from July 2015 to February 2017 to determine if they have the underlying data for these figures. EPA has not received responses from many of the authors as of the date of release of this document.

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assessed using the ADHD subscale of the Child Behavior Checklist (CBCL), which was completed by mothers. A total of 271 children were initially assessed at 6 months, and 207 were assessed at 5 years. Chevrier et al. (2011) used multiple linear regression models to determine the relationship between thyroid hormone levels in the second trimester and neurodevelopmental outcomes. Thyroid hormone levels were assessed as a continuous measure and as dichotomous variables, using cut points of the 10th and 90th percentiles. Models were adjusted for various parameters that may have an impact on cognitive performance, such as maternal age, diet quality, and blood lead levels.

Overall, the associations between maternal thyroid levels and children's scores on the BSID were consistently negative (i.e., higher fT4 is associated with lower score on the BSID) and thus in the opposite of the expected direction; however, these results were not statistically significant. At age 5, only one significant association with maternal thyroid levels was observed: scores on the ADHD subscale of the CBCL decreased by 0.65 points per doubling of maternal TSH. However, no associations with maternal thyroid levels were observed in any of the other attention measures studied. A summary of the key results is presented in Table 12. The authors concluded that the likely reason for the observed lack of association is that thyroid hormone levels were assessed during late pregnancy; prior research has reported associations between neurodevelopment and maternal thyroid hormone levels in the first trimester. As the study authors state, "thyroid hormone of maternal origin may thus be of particular importance to brain development before the onset of fetal thyroid function, which occurs around midgestation" (p. 7). It is also possible that alterations in thyroid hormones in later trimesters of pregnancy may result in neurodevelopmental effects not captured by the BSID.

Table 12. Summary of Results[a] Evaluating the Relationship Between fT4 Levels and Neurodevelopment at Various Ages

Age	Bayley Scales MDI: β (95% CI)	Bayley Scales PDI: β (95% CI)	Performance IQ: β (95% CI)
6 Months	-3.14 (-7.65, 1.36)	-3.27 (-9.36, 2.82)	N/A
12 Months	-0.48 (-6.22, 5.26)	-6.40 (-13.89, 1.08)	N/A
24 Months	-4.29 (-11.60, 3.02)	-2.67 (-8.95, 3.62)	N/A
5 Years	N/A	N/A	-4.12 (-13.73, 5.49)

Source: Chevrier et al. (2011, Table 4).
[a] fT4 levels were measured in ng/dL.

Key finding: Results of the analysis did not find a significant relationship between maternal thyroid hormone levels during the second trimester of pregnancy and performance on the Bayley Scale or IQ tests.

Detailed Summary of Finken et al. (2013)

Maternal Hypothyroxinemia in Early Pregnancy Predicts Reduced Performance in Reaction Time Tests in 5- to 6-Year-Old Offspring

Finken et al. (2013) aimed to investigate the association between maternal fT4 and TSH concentrations and children's neurodevelopment, using a large, population-based cohort. Participants were recruited from pre-natal clinics in Amsterdam and excluded from the study if mothers used thyroid inhibitors during pregnancy or if children had congenital abnormalities. fT4 and TSH were

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measured once during pregnancy at a median gestational age of 12.9 weeks, and childhood cognitive performance was assessed 5 to 6 years later. TPO Ab positivity was also measured. The authors used the Amsterdam Neuropsychological Test (ANT) computerized assessment program, which consists of a series of tests to measure cognitive functioning such as reaction time and visuomotor coordination. Full biomarker and assessment data were available for 1,765 mother-child pairs. Since fT4 levels showed a slight negative association with gestational day, concentrations were standardized for the day of sampling. Linear regression models were constructed with adjustment for covariates including age, gender, demographic characteristics (e.g., birth order, ethnicity), and pregnancy characteristic (e.g., BMI and diabetes). Finken et al. (2013) also compared children with and without hypothyroxinemia (< 10th percentile of fT4) and hyperthyrotropinemia (> 90th percentile of TSH) and examined interactions between the two. The authors additionally performed analyses after excluding subjects born pre-term (< 32 GW), with very low birthweight (< 1,500 g), or test results ± 3 SD from the mean as a result of poor comprehension or motivation. TPO Ab-positive mothers were included in the main analysis, but a separate analysis found TPO Ab positivity was not related to any of the outcomes in Table 13.

In all regression models tested, maternal fT4 levels were inversely associated with reaction time SD within an individual in a reaction time task. Maternal hypothyroxinemia was significantly associated with higher baseline reaction time when compared to non-hypothyroxinemic mothers (fT4 ≥ 10th percentile at the first prenatal visit). Specifically, there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time, when comparing the offspring of hypothyroxinemic to non-hypothyroxinemic mothers. Finken et al. (2013) also found an association between hypothyroxinemia (as defined as fT4 < 10th or < 5th percentiles) and increased mean reaction time and reaction time SD. While mean reaction time is a general measure of speed, reaction time SD reflects the consistency of performance across time. The authors noted that mean reaction time SD outcome "…has been found to be related more strongly to individual difference in intelligence, cognitive aging, and neurological disorders" than reaction time itself (Finken et al., 2013, p. 1419). While no associations between hyperthyrotropinemia and reaction test performance were observed, there was an interaction between hypothyroxinemia and hyperthyrotropinemia; children of mothers with both conditions had a significantly greater reaction time mean and SD. Associations between maternal fT4 or TSH and other ANT outcomes (e.g., visuomotor coordination) were not observed. Results from the study are summarized in Table 13. Results remained similar in the additional analyses after excluding subjects.

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Table 13. Summary of Results Evaluating the Relationship between Thyroid Hormones and Developmental Outcomes in Finken et al. (2013)

Test	Predictor	β (95% CI)	P
Baseline Speed			
Mean reaction time, milliseconds	fT4 (pmol/L)	-4.5 (-9.0; 0.1)	0.06
	TSH (mU/L)	2.3 (-1.3; 5.9)	0.21
Reaction time, SD, milliseconds	fT4 (pmol/L)	-4.9 (-9.5; -0.2)	0.04
	TSH (mU/L)	1.0 (2.7; 4.6)	0.61
Pursuit			
Deviation, millimeters	fT4 (pmol/L)	-0.01 (-0.22; 0.21)	0.95
	TSH (mU/L)	0 (-0.17; 0.17)	0.99
SD of deviation, millimeters	fT4 (pmol/L)	0 (-0.20; 0.21)	0.97
	TSH (mU/L)	0.04 (-0.12; 0.20)	0.65
Tracking			
Mean distance, millimeters	fT4 (pmol/L)	-0.01 (-0.11; 0.09)	0.78
	TSH (mU/L)	0.04 (-0.05; 0.11)	0.40
Accuracy stability, millimeters	fT4 (pmol/L)	0.04 (-0.06; 0.15)	0.42
	TSH (mU/L)	0.01 (-0.08; 0.09)	0.84
Movement speed, seconds	fT4 (pmol/L)	-0.08 (-0.34; 0.18)	0.55
	TSH (mU/L)	0.10 (-0.11; 0.31)	0.34
Response Organization Objects			
Part 1 (compatible)			
Mean reaction time, milliseconds	fT4 (pmol/L)	-5.1 (-12.1; 1.8)	0.15
	TSH (mU/L)	1.4 (-4.0; 7.0)	0.61
Reaction time, SD, milliseconds	fT4 (pmol/L)	-1.7 (-7.4; 3.9)	0.55
	TSH (mU/L)	4.6 (0.1; 9.1)	0.05
Part 2 (incompatible)			
Mean reaction time, milliseconds	fT4 (pmol/L)	2.0 (-7.6; 11.6)	0.69
	TSH (mU/L)	4.6 (-3.1; 12.3)	0.24
Reaction time, SD, milliseconds	fT4 (pmol/L)	0.9 (-6.7; 8.6)	0.82
	TSH (mU/L)	7.3 (1.2; 13.3)	0.02

Source: Finken et al. (2013, Table 3).
Note: Results adjusted for gender and age at assessment, family background variables, including computer gaming (< 1 or ≥ 1 hr/day); birth order; maternal education (in 4 categories); ethnicity (Western or non-Western); and pregnancy characteristics, including maternal age, BMI, diabetes (yes or no), and hypertension (yes or no).

Key finding: Maternal fT4 levels at a median of 12.9 weeks were inversely associated with the reaction time variability among 5- to 6-year-old children (an increase in the reaction time SD of 4.9 ms was associated with every 1 pmol/L reduction in maternal fT4). Considering fT4 as a categorical variable demonstrated that there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time, when comparing the offspring of hypothyroxinemic to non-hypothyroxinemic mothers.

Detailed Summary of Gyllenberg et al. (2016)

Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort

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Gyllenberg et al. (2016) examined the relationship between maternal thyroid deficiency during gestation and schizophrenia in offspring with a nested case-control study. Retrospective study data were obtained from the Finnish Prenatal Study of Schizophrenia (FiPS-S), a subset within the Finnish Maternity Cohort (FMC). The FMC contains archived maternal blood samples from most pregnancies in Finland since 1983. Offspring in the cohort with schizophrenia or schizoaffective disorder (both referred to as schizophrenia hereafter) were identified using the Finnish Hospital and Outpatient Discharge Register and were included if they were within the age of risk for schizophrenia. For this study, records were included if the individual was diagnosed at 26 years old or less before December 31, 2009. The national hospital and outpatient information recorded diagnoses for psychiatric hospital admissions and psychiatric outpatient treatment visits and was obtained for FiPS-S participants. Maternal fT4 and TSH were measured via blood samples drawn during the first trimester or early second trimester (2-4 months of pregnancy). TPO Ab was not measured. Blood samples were excluded if they contained HIV, syphilis, or hepatitis. After cases of schizophrenia were identified, they were matched 1:1 with control subjects. Control subjects were drawn randomly from the FMC if they did not have schizophrenia or other psychotic disorders. Maternal blood serum samples of 1,010 case-control pairs were assessed for fT4, and 948 case-control pairs were assessed for TSH. Maternal thyroid deficiencies measured included hypothyroxinemia (classified as fT4 $\leq 10^{th}$ percentile and TSH outside of the 5th-95th percentile), hypothyroidism, subclinical hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism.

Chi squared, Fisher's exact, and *t* tests were used to evaluate relationships between covariates, thyroid hormones, and schizophrenia. fT4 levels were log-transformed before being analyzed as continuous variables to correct the skewness of the data. Categorical transformation of continuous variables allows maternal thyroid disorder data to be interpreted using logistic regression models.

Maternal hypothyroxinemia was associated with an increased odds of schizophrenia in offspring (OR = 1.75; 95% CI: 1.22-2.50, $p = 0.002$). The proportion of subjects with maternal hypothyroxinemia was 11.8% among schizophrenic subjects compared with 8.6% among control subjects. This association remained significant after adjusting for maternal psychiatric history, province at birth, and maternal smoking status (OR = 1.70; 95% CI: 1.13-2.55; $p = 0.010$).

Defining maternal fT4 as a continuous variable, there was a linear association between log units of maternal fT4 and log odds of schizophrenia in offspring. A conditional logistic regression analysis revealed that the odds of schizophrenia decreased by almost 50% per log unit increase of maternal fT4 (OR = 0.54; 95% CI: 0.31-0.94; $p = 0.028$) (Table 14). This relationship remained significant after adjusting for maternal psychiatric history and province of birth. However, after individually adjusting for maternal smoking during early gestation and collectively adjusting for maternal psychiatric history, province of birth, and maternal smoking, the association between maternal hypothyroxinemia and offspring schizophrenia was no longer significant (Table 14). The adjustment for maternal smoking resulted in a greater than 20% change in the odds ratio. According to the authors, "this finding suggests that the relationship between maternal fT4 and schizophrenia is present only when fT4 levels are below a particular threshold" (p. 966, defined in this study as under the 10th percentile of the distribution). The association between log-transformed TSH and schizophrenia was not significant. In analyzing for potential mediators in the association between hypothyroxinemia and schizophrenia, pre-term birth and birthweight both decreased the odds ratios, and the *p*-value was no longer significant.

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Table 14. Summary of Results Regarding the Association Between Maternal Hypothyroxinemia and Offspring Schizophrenia

Model	Odds Ratio (95% CI)	*p-value*
Categorical Hypothyroxinemia[a] During Early Gestation		
Unadjusted	1.75 (1.22-2.50)	0.002
Individually adjusted for maternal psychiatric history	1.92 (1.30-2.83)	0.001
Individually adjusted for province of birth	1.78 (1.23-2.57)	0.002
Individually adjusted for maternal smoking during early gestation[b]	1.62 (1.12-2.37)	0.012
Adjusted for maternal psychiatric history, province of birth, and maternal smoking	1.70 (1.13-2.55)	0.010
Log-Transformed fT4 During Early Gestation		
Unadjusted	0.54 (0.31-0.94)	0.028
Individually adjusted for maternal psychiatric history	0.53 (0.30-0.94)	0.029
Individually adjusted for province of birth	0.57 (0.33-0.999)	0.049
Individually adjusted for maternal smoking during early gestation[b]	0.71 (0.39-1.27)	0.243
Adjusted for maternal psychiatric history, province of birth, and maternal smoking	0.74 (0.40-1.38)	0.342

Source: Gyllenberg et al. (2016).
[a] Defined at fT4 ≤ 14.03 pmol/L (≤10th percentile) and TSH > 0.24-3.38 mIU/L (> 5th-95th percentile).
[b] Based on log-transformed cotinine levels, a metabolite of nicotine and biomarker of smoking, in maternal sera from FMC.

Key finding: An association between fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range) and odds of schizophrenia diagnosis was found using conditional logistic regression. However, this relationship was attenuated after controlling for smoking. Considering fT4 as a categorical variable demonstrated that 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.

Detailed Summary of Ghassabian et al. (2014)

Downstream Effects of Maternal Hypothyroxinemia in Early Pregnancy: Nonverbal IQ and Brain Morphology in School-Age Children

Ghassabian et al. (2014) aimed to examine whether children born to mothers with hypothyroxinemia during early pregnancy would show decreased nonverbal IQ at 6 years of age. Along with reductions in IQ, Ghassabian et al. (2014) hypothesized that children of hypothyroxinemic mothers would display corresponding structural changes in the size of several key areas of the brain: the cortex, hippocampus, and corpus callosum. An additional aim was to investigate the relationship between subclinical hypothyroidism (normal fT4 and high TSH) in mothers and IQ in children. Participants (n = 3,727) were recruited from the Generation R birth cohort in the Netherlands; all singleton births with complete information on maternal thyroid levels and children's nonverbal IQ at age 6 were included in the study. A subset of children participating in the study (n = 652) underwent MRI testing to assess volume of various brain regions. Maternal thyroid function (fT4, TSH, and TPO Ab) were measured at a mean of 13.5 GW. Hypothyroxinemia was defined as fT4 levels below 10.99 pmol/L (the 5th percentile of the sample) and subclinical hypothyroidism as normal fT4 and high TSH

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(defined as TSH > 2.5 mIU/L or > 3.0 mIU/L). Children completed a well-validated Dutch nonverbal intelligence test (the Snijders-Oomen Niet-Verbale Intelligentie test), which consisted of mosaics to assess spatial visualization skills and categories to assess abstract reasoning skills. Linear regression models were used to investigate the association between maternal thyroid function and children's nonverbal IQ and brain volumetric measures. Maternal fT4 and TSH were divided by their SD in the regression analyses to determine the impact of SD increments or decrements in these parameters. Regression analyses with IQ as the outcome were adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.

Ghassabian et al. (2014) did not find an association between continuous measures of maternal thyroid function (fT4, TSH, and TPO Ab positivity) and children's IQ at the age of 6 years. An analysis of continuous fT4 and its relationship with IQ in just the children of hypothyroxinemic mothers was not conducted. However, Ghassabian et al. (2014) did find that children of mothers with hypothyroxinemia scored an average of 4.3 IQ points lower ($p = 0.001$, 95% CI: -6.68, -1.81) on IQ tests than children of mothers with thyroid function within the population reference range. No significant associations were found between maternal hypothyroxinemia and any of the brain volume measures assessed. Maternal subclinical hypothyroidism did not show a significant relationship with children's IQ. A summary of results can be found in Table 15.

Table 15. Summary of Results from Ghassabian et al. (2014)

Maternal Thyroid Function	Child's IQ at 6 years of age		
	β	95% C.I.	*p*-value
TSH per SD	0.04	-0.17, 0.26	0.70
fT4 per SD	-0.24	-0.61, 0.14	0.21
Hypothyroxinemia	-4.32	-6.68, -1.81	**0.001**

Source: Ghassabian et al. (2014), Table 2.
Models were adjusted for child's ethnic background and birth order and maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology in pregnancy, household income, and time of blood sampling in pregnancy. Hypothyroxinemia (n = 129): 0.03 < TSH < 2.5 mIU/L and fT4 < 10.99 pmol/L (less than the 5th percentile).

Key Finding: Maternal hypothyroxinemia during early pregnancy (mean GW = 13.5) was associated with an average reduction of 4.3 points ($p = 0.001$, 95% CI: -6.68, -1.81) in children's nonverbal IQ at age 6. Continuous measures of maternal thyroid function (TSH, fT4) across the entire range (not the hypothyroxinemic range) and subclinical hypothyroidism were not significantly associated with nonverbal IQ in 6-year-old children.

Detailed Summary of Henrichs et al. (2010)

Maternal Thyroid Function during Early Pregnancy and Cognitive Functioning in Early Childhood: The Generation R Study

Henrichs et al. (2010) evaluated the relationship between early pregnancy TSH and fT4 levels in mothers and cognitive functioning of their children in a Netherlands-based study. Participants were recruited from a birth cohort and excluded if T4 treatment was received during pregnancy. Maternal blood was analyzed for fT4 and TSH at a mean GW of 13.3. TPO Abs were not measured. Mothers

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were classified as having mild or severe hypothyroxinemia based on T4 levels < 10th (< 11.76 pmol/L) and < 5th percentiles (< 10.96 pmol/L), respectively. Parents completed several questionnaires to assess verbal development at age 18 months and verbal and nonverbal development at 30 months. Verbal assessments at 18 and 30 months (the MacArthur Communicative Development Inventory and the Language Development Inventory, respectively) consisted of checklists of words; parents identified words spontaneously spoken by children, which were then summed to derive age- and gender-specific percentiles. Expressive language delay at age 18 or 30 months was operationalized as scores below the 15th percentile. Delay at 30 months was also indicated by a lack of word combinations (i.e., the child had not begun to construct phrases). Nonverbal cognitive development was assessed using the Parent Report of Children's Abilities, which consists of questions to parents (e.g., on spatial ability, memory, and planning skills) and parent-administered tasks (e.g., building blocks). Cognitive delay was similarly defined as scores below the 15th age- and gender-specific percentiles. Logistic regression analyses were conducted with adjustment for maternal age, education, pre-natal distress, pre-natal smoking, birthweight, gestational age at blood sampling, and child ethnicity.

Results indicated that, while maternal TSH was not found to be related to the cognitive outcomes measured, maternal fT4 was found to be inversely related to expressive language delay at 30 months of age. Both mild and severe maternal hypothyroxinemia were found to be associated with a higher risk of expressive language delay across the age range of 18 months (OR = 1.44; 95% CI: 1.09, 1.91; $p = 0.010$) and 30 months of age (OR = 1.80; 95% CI: 1.24, 2.61; $p = 0.002$), respectively. Henrichs et al. (2010) also reported that severe hypothyroxinemia in the mothers was associated with a 2.03-fold increased risk of nonverbal cognitive delay in their children (95% CI: 1.22, 3.39, $p = 0.007$). The authors also found that fT4 levels per SD were associated with a higher risk of expressive language delay at 30 months (OR = 0.84, 95% CI: 0.71, 0.99). The SD specifically associated with this finding is not reported in Henrichs et al. (2010).[14] The findings of this study, summarized in Table 16, indicate that children born to mothers with hypothyroxinemia are at an increased risk of cognitive delays in early childhood.

Table 16. Summary of Results from Henrichs et al. (2010)

Maternal Thyroid Function Measure	Expressive Language Delay at 18 Months		Expressive Language Delay at 30 Months		Expressive Language Delay at 18 and 30 Months		Nonverbal Cognitive Delay at 30 Months	
	n	OR (95% CI) *p*-value	n	OR (95% CI) *p*-value	n	OR (95% CI) *p*-value	n	OR (95% CI) *p*-value
TSH, per SD	3384	0.91 (0.81; 1.03) 0.136	2757	0.92 (0.81; 1.06) 0.249	3614	0.92 (0.84; 1.02) 0.100	2588	0.98 (0.88; 1.10) 0.759
fT4, per SD	3409	0.95 (0.83; 1.09) 0.430	2779	0.84 (0.71; 0.99) **0.039**	3643	0.90 (0.80; 1.01) 0.069	2606	0.85 (0.72; 1.01) 0.057
Mild hypothyroxi-nemia	2736	1.33 (0.91; 1.94) 0.143	2225	1.47 (1.00; 2.17) 0.051	2926	1.44 (1.09; 1.91) **0.010**	2086	1.37 (0.90; 2.07) 0.139

[14] Study authors were contacted on November 18, 2016, for this information and have not yet responded.

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Maternal Thyroid Function Measure	Expressive Language Delay at 18 Months		Expressive Language Delay at 30 Months		Expressive Language Delay at 18 and 30 Months		Nonverbal Cognitive Delay at 30 Months	
Severe hypothyroxi-nemia	2736	1.77 (1.10; 2.84) **0.018**	2225	1.78 (1.07; 2.94) **0.024**	2926	1.80 (1.24; 2.61) **0.002**	2086	2.03 (1.22; 3.39) **0.007**
Source: Henrichs et al. (2010, Tables 2 and 3).								

Key Finding: Severe maternal hypothyroxinemia was associated with expressive language delay at 18 and 30 months and non-cognitive delay at 30 months. Further, there was an increase in the odds of expressive language delay and non-cognitive delay when comparing the offspring of children exposed to mild versus severe maternal hypothyroxinemia, suggesting a potential dose-response between the severity of hypothyroxinemia and expressive language delay and non-cognitive delay. Additionally, maternal fT4 levels per SD were associated with a reduction in odds of expressive language delay at 30 months (OR = 0.84 per SD of fT4).

Detailed Summary of Korevaar et al. (2016)

Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study

Korevaar et al. (2016) examined the relationship between maternal thyroid function, child IQ, and brain morphology. Maternal thyroid function data, including TSH, fT4, and TPO Ab, were assessed at 9-18 weeks of pregnancy. Child IQ was assessed between 5.6 and 7.9 years of age using a Dutch non-verbal intelligence test with high reliability (the Snijders-Oomen Niet-Verbale Intelligentie Test). The IQ test assesses a broad range of language-independent intelligence functions such as spatial visualization abilities and abstract reasoning abilities. Child brain morphology was assessed using structural MRI brain scans. Pregnant mothers were recruited if they lived in the municipality of Rotterdam, Netherlands, and were enrolled as participants in the Generation R Study. The main exclusion criteria for mother-child pairs were abortion, fetal loss, or gestational age of 24 weeks or more at the start of the study. Additional exclusion criteria for mother-child pairs undergoing the IQ assessment were twin pregnancies, pre-existing thyroid disease, concomitant medication that affects thyroid function, fertility treatment, or IQ scores ≤50. After exclusion criteria were applied, 3,839 mother-child pairs constituted the IQ study population, and 646 were included in the brain morphology study population (598 mother-child pairs overlapped between the two analyses). TSH and fT4 were log-transformed and then evaluated for associations with child IQ or brain morphology MRI outcomes using ordinary least-squares linear regression models with restricted cubic splines with knots at the 10th, 50th, and 90th percentiles. Effect estimates were reported from multivariate linear regression models with a quadratic term that approximated the model curves developed in the spline analysis. In analyses of IQ, models were adjusted for potential confounders including gestational age, maternal age, smoking, BMI, parity, education level, ethnic origin, fetal sex, and birthweight. Analyses of brain morphology were adjusted for gestational age, maternal age, BMI, child age, sex, birthweight, and gestational age at birth. All analyses were adjusted for chorionic gonadotropin, TPO Ab, and child thyroid function.

Selected study results are included in Figure 7. Overall, analysis results between maternal fT4 and offspring IQ showed an inverted U-shaped association (p = 0.0044 in the whole population (Figure 7

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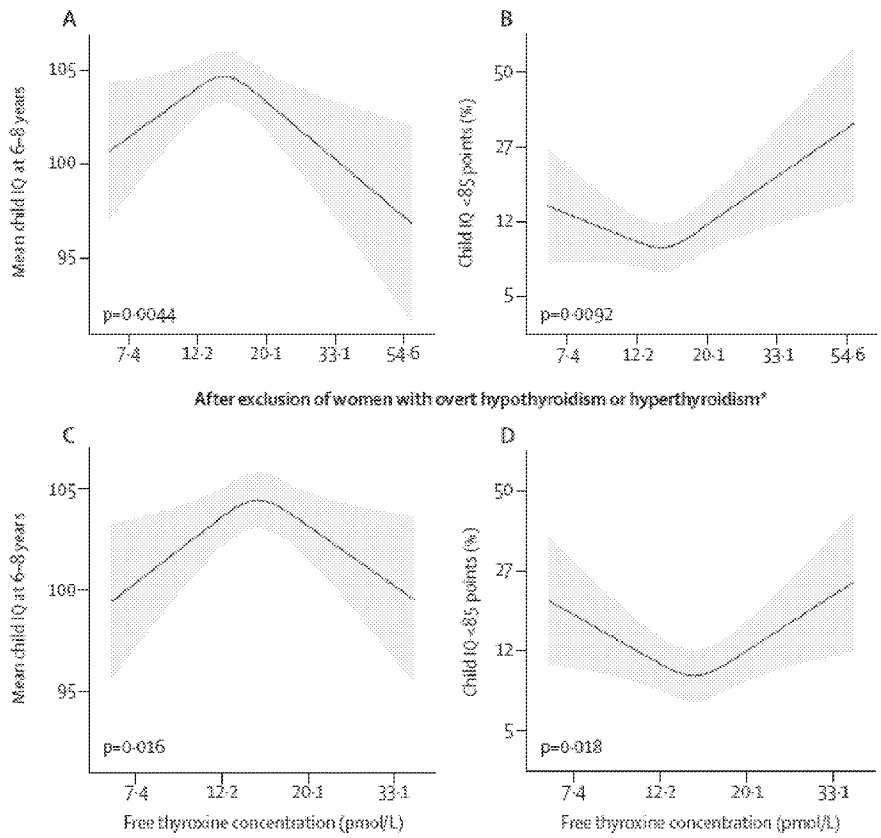
A); $p = 0.016$ after exclusion of women with overt hypothyroidism or hyperthyroidism (Figure 7 C)). All associations remained similar after adjusting for concentrations of human chorionic gonadotropin, child TSH and fT4, or maternal TPO Ab. Associations remained significant after the exclusion of cases of overt hypothyroidism and overt hyperthyroidism, which implies that changes in fT4 in the subclinical range can affect IQ (Korevaar et al., 2016). Korevaar et al. (2016) found that the relationship demonstrated in the spline model (Figure 7) was well explained by the multivariate linear regression analysis with a quadratic term, as summarized in Table 17.

Further, high maternal fT4 (range of cut points: > 88th to > 97th percentile) corresponded to a 1.4 to 3.7 point reduction in mean offspring IQ when compared to the reference group (fT4 between 10th and 90th percentile). Low maternal fT4 (range of cut points: < 3rd to < 11th) corresponded to a 1.5 to 3.8 point loss when compared to the reference group.

For the MRI portion of the study, associations with maternal fT4 showed a U-shaped association for mean child gray matter volume ($p = 0.0062$ in the whole population; $p = 0.011$ after exclusion of women with overt hypothyroidism or hyperthyroidism) and for mean cortex volume ($p = 0.0011$ in the whole population; $p = 0.0016$ after exclusion of women with overt hypothyroidism or hyperthyroidism).

Figure 7. Association between Maternal Free Thyroxine and Offspring IQ



(A, C) Association between maternal fT4 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 fT4 levels during pregnancy and the risk of child IQ below 85 as predicted by 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

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between the upper and lower graphs because of exclusions of women with overt, but not subclinical, disease entities. *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 (Korevaar et al., 2016).

Table 17. Summary of Results Evaluating the Relationship Between Maternal fT4 levels with Mean Child IQ

Variables in Model	IQ: β (95% CI) [b]
fT4	33.81 (9.8, 57.82) [a]
$fT4^2$	-6.235 (-10.567, -1.903) [a]

[a] Statistically significant at $p<0.05$

[b] Reported beta and 95% confidence interval are increase in IQ per log increase in fT4. 95% confidence intervals were calculated by multiplying standard error of 12.25 for fT4 and 2.210 for $fT4^2$ presented in Korevaar et al. (2016) by 1.96. $fT4^2$ refer to addition of a squared fT4 variable in the model. Analyses were performed using linear regression models in N=3,839 mother-child pairs. fT4 values were transformed by the natural logarithm.

Source: Korevaar et al. (2016)

Key finding: The authors concluded that both low and high maternal fT4 concentrations during pregnancy were associated with lower child IQ and lower gray matter and cortex volume.

Detailed Summary of Modesto et al. (2015)

Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children

Modesto et al. (2015) examined the relationship between exposure to maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder (ADHD) in offspring at 8 years of age. Maternal thyroid function data, including TSH, fT4, and TPO Abs, were assessed during the first or second trimester at a mean of 13.6 (range 6.6-17.9) weeks of gestation. Mothers using the Conners' Parent Rating Scale-Revised Short Form assessed children's ADHD at 8 years of age. This assessment includes the four scales: Cognitive Problems/Inattention, Hyperactivity, Oppositional, and the ADHD index (ADHDi). The possible range of scores for this test is 0-36 with higher scores indicating more ADHD symptoms. Maternal hypothyroxinemia was defined as TSH levels within the population reference range (0.1 to 2.5 mIU/L) and low fT4 levels below the 5th percentile of the sample (< 0.85 ng/dL = 10.94 pmol/L). Positive results for TPO Abs were defined as plasma concentrations 100 IU/mL or greater. Pregnant mothers were recruited if they lived in the municipality of Rotterdam, Netherlands, and were in the Generation R Study. The main exclusion criteria for mother-child pairs were birth of twins, availability of thyroid hormone data, and if no return assessment occurred of child with mother (or caregiver) by 6 years of age of the child.

Continuous measures of TSH and fT4 were divided by their standard deviations to easily compare their associations with outcomes (Table 18). The authors examined associations between maternal thyroid function (across the entire range of fT4, not just the hypothyroxinemic range) with a child's ADHDi and Oppositional scores using linear regression. To satisfy the assumption of normality, these scores were transformed using natural logarithms. Regression coefficients were subsequently exponentiated and converted to percentage differences. Models were adjusted for the possible confounders of child age, sex, ethnic background, and parity, and maternal education level, smoking

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history, psychopathologic symptoms in pregnancy, age, marital status, household income, BMI, and gestational age at the time of blood sampling for maternal thyroid function data. Models were additionally adjusted for the following potential confounders in separate steps to test specificity of the findings: child's autistic symptoms, nonverbal IQ, Oppositional scores, or ADHDi scores.

In general, children of mothers with maternal hypothyroxinemia (127 mothers) in early pregnancy had higher ADHDi scores at 8 years old when compared to children without exposure to maternal hypothyroxinemia, after adjusting for the factors described above (7% increase in ADHDi scores (95% CI: 0.3%-15%)). Additional adjustments for a child's autistic symptoms or Oppositional scores did not affect this association. The results remained mostly unchanged when women with elevated TPO Abs were excluded. A separate analysis focusing on a fetal gestational age of less than 13 weeks at the time of sampling found statistically significant associations, after adjusting for age and sex, between maternal hypothyroxinemia and ADHDi scores ($\beta = 0.15$; 95% CI: 0.01, 0.28; $p = 0.04$) and between fT4 and ADHDi scores ($\beta = -0.02$; 95% CI: -0.04, -0.001; $p = 0.04$) at 8 years of age. However, when fully adjusted (for child age, sex, and ethnic background and maternal educational level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, BMI, and time of blood sampling in pregnancy), the relationship between fT4 and ADHDi scores was no longer statistically significant ($\beta = -0.02$; 95% CI: -0.03, 0.003; $p = 0.10$). No associations were found between maternal subclinical hypothyroidism and ADHDi score in children; and maternal thyroid function in early pregnancy and children's Oppositional scores at 8 years of age.

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Table 18. Summary of Results[a] Evaluating the Relationship Between Maternal Thyroid Function in Early Pregnancy and Children's ADHDi Scores at 8 Years of Age

Thyroid Function Variable	Parent-Reported ADHDi Score: β (95% CI)	Changes in Scores, % (95% CI)
Maternal Hypothyroxinemia[b]		
Unadjusted	0.08 (0.01, 0.15)[d]	8 (1, 16)
Adjusted for age and sex	0.08 (0.01, 0.15)[d]	8 (1, 16)
Fully adjusted model[c]	0.07 (0.003, 0.14)[d]	7 (3, 15)
Free T4 Level per Standard Deviation[e]		
Unadjusted	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Adjusted for age and sex	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Fully adjusted model[c]	-0.01 (-0.02, 0.01)	-1 (-2, 1)
TSH Level per Standard Deviation[f]		
Unadjusted	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Adjusted for age and sex	-0.01 (-0.02, 0.003)	-1 (-2, 0.3)
Fully adjusted model[c]	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Maternal Hypothyroxinemia (TSH cut point 0.03-4.04 mIU/L)[b]		
Unadjusted	0.05 (-0.01, 0.11)	5 (-1, 12)
Adjusted for age and sex	0.05 (-0.01, 0.11)	5 (-1, 12)
Fully adjusted model[c]	0.05 (-0.01, 0.11)	5 (-1, 12)
Maternal Hypothyroxinemia (gestational age < 13 weeks at time of sampling)[b]		
Unadjusted	0.17 (0.03, 0.31)[d]	18 (3, 36)
Adjusted for age and sex	0.15 (0.01, 0.28)[d]	16 (1, 32)
Fully adjusted model[c]	0.13 (-0.01, 0.26)	14 (-1, 29)
Free T4 Level per Standard Deviation (gestational age < 13 weeks at time of sampling)[e]		
Unadjusted	-0.02 (-0.04, -0.004)[d]	-2 (-4, -0.4)
Adjusted for age and sex	-0.02 (-0.04, -0.001)[d]	-2 (-4, -0.1)
Fully adjusted model[c]	-0.02 (-0.03, 0.003)	-2 (-3, 0.3)
TSH Level per Standard Deviation (gestational age < 13 weeks at time of sampling)[f]		
Unadjusted	-0.004 (-0.02, 0.01)	-0.4 (-2, 1)
Adjusted for age and sex	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Fully adjusted model[c]	-0.004 (-0.02, 0.01)	-0.4 (-2, 1)

Source: Modesto et al. (2015).
[a] Results are presented in ng/dL unless otherwise noted.
[b] Categorical analysis.
[c] Adjusted for child age, sex, and ethnic background and maternal educational level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, BMI, and time of blood sampling in pregnancy.
[d] Statistically significant at $p < 0.05$.
[e] The SD for fT4 is 0.29 ng/dL.
[f] The SD for TSH is 1.3 mIU/L.

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Key finding: Maternal hypothyroxinemia in early pregnancy was associated with higher ADHDi scores in 8-year-old children compared with non-exposed children, after adjusting for confounders (7% increase in ADHDi scores (95% CI: 3%-15%)). When considering fT4 as a continuous variable, the association between maternal fT4 and offspring ADHDi scores was attenuated with the adjustment of confounders.

Detailed Summary of Moleti et al. (2016)

Effects of Maternal Iodine Nutrition and Thyroid Status on Cognitive Development in Offspring: A Pilot Study

Moleti et al. (2016) examined the effects of maternal iodine and/or levothyroxine (LT4) supplementation on the IQ of their offspring. This prospective, observational study included four study groups of 15 mother-child pairs from a small rural area in northeastern Sicily. The groups were iodine (I); no iodine (no-I); iodine + LT4 (I + T4); and no iodine + LT4 (no-I + T4). Pregnant mothers were sampled for fT3, fT4, TSH, TPO Ab (considered positive if values > 34 IU/mL), and antithyroglobulin (TgAb) starting at GW < 12 weeks and continuing every 6 weeks throughout pregnancy. To be included in the iodine groups, women had to have regularly consumed iodized salt up to 2 years prior to pregnancy and continued consumption during pregnancy. For the no-iodine groups, women were excluded if they had regular iodized salt consumption prior to pregnancy or consumed iodized salt upon becoming pregnant. Other inclusion criteria for mothers included age greater than 18 years, an uncomplicated singleton pregnancy, (full) term delivery, no severe or chronic diseases (including thyroid autoimmune diseases), no major post-partum complications, and full disclosure of diet and lifestyle information during and after pregnancy. Inclusion criteria for children included age 6 to 14 years, no major neonatal complications, no congenital hypothyroidism, no severe/chronic diseases or cognitive deficits, and regular school attendance. Children ages 6 to 12 years of age were administered IQ tests blind by trained psychologists with the WISC-III, full-scale IQ (FSIQ), verbal IQ, and performance IQ (PIQ). Full-scale IQ scores of 70-85 were considered to be suggestive of borderline defective cognitive function and scores less than 70 were considered to be suggestive of defective cognitive function.

Statistical analyses were performed using the Mann-Whitney (comparison of independent samples), Wilcoxon (comparison of dependent samples), and Friedman (comparison over the observation period of several dependent groups) tests. A chi-squared (χ^2) test was used to evaluate the association between categorical variables. Logistic regression models were used to evaluate the dependence of suboptimal cognitive outcomes (IQ scores less than 85) on various explanatory variables and confounders. Covariates assessed in the models included maternal age; gestational age at birth; birthweight; child age at time of IQ test; maternal fT4, and TSH various times during gestation; maternal urinary iodide excretion; family socioeconomic status; maternal parity; sex of child; breastfeeding; major maternal stressful life-events; and maternal/parental education.

Overall, mothers in the iodine groups had significantly higher fT4 concentrations than those in the no-iodine groups. In this study, fT4 was evaluated across the entire range of pregnancy and fT4 concentrations, and not solely the hypothyroxinemic range in early pregnancy. The overall prevalence of borderline or defective cognitive function was more than three-fold higher in offspring of mothers not using iodized salt compared to mothers using it (76.9% vs. 23.1%, OR = 7.667, 95% CI: 2.365-24.856; $\chi^2 = 12.65$; $p = 0.0001$). Children born to mothers in the iodine group had significantly higher FSIQ and VIQ scores compared to the no-iodine offspring (FSIQ: (I) 93.1 ± 11.8 vs. (no-I) 81.7 ±

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13.5, $p = 0.028$; VIQ (I) 90.1 ± 14.2 vs. (no-I) 80.3 ± 12.3, $p = 0.034$). Similar differences were found between I+T4 and no-I + T4 offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and FSIQ, but failed to reach statistical significance (Table 19). Given the small sample size in the study, the authors caution against firm conclusions being drawn from their analysis. Additionally, the design of the study did not include parental IQ testing (a possible confounder for child IQ). The hypothesis set forward by the authors for the results of their analysis, which show iodine to be a more important predictor of neurodevelopmental outcomes compared to thyroid hormone levels, is that the fetus is being exposed to insufficient amounts of thyroid hormone as a result of not having enough iodine from the mother to develop its own thyroid hormones.

Table 19. Relationship Between Cognitive Outcomes and fT4 (Univariate Logistic Regression Models)

	VIQ: exp β (95% CI)	PIQ: exp β (95% CI)	FSIQ: exp β (95% CI)
Gestational weeks of fT4 measurement			
≤12 weeks	1.192 (0.980-1.450)	1.053 (0.881-1.259)	1.103 (0.928-1.311)
13 - 18 weeks	1.217 (1.015-1.459)[a]	1.010 (0.855-1.194)	1.165 (0.980-1.385)
19 - 24 weeks	1.234 (0.991-1.537)	1.125 (0.897-1.411)	1.155 (0.937-1.425)
25 - 30 weeks	1.137 (0.928-1.393)	1.003 (0.810-1.243)	1.031 (0.847-1.254)
Week 31 - term	1.191 (0.982-1.445)	1.010 (0.834-1.224)	1.070 (0.895-1.280)
Maternal urinary iodide concentration			
	1.017 (1.001-1.033)[b]	1.012 (0.995-1.028)	1.013 (0.998-1.029)

Source: Moleti et al. (2016).
[a] 95% CI interval suggests statistical significance, but significance for this result and most results in this table were not denoted in the study.
[b] Statistically significant at $p < 0.05$.

Key finding: The authors found that maternal iodine status is predictive of neurodevelopmental outcomes in offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and FSIQ, but failed to reach statistical significance.

Detailed Summary of Noten et al. (2015)

Maternal Hypothyroxinemia in Early Pregnancy and School Performance in 5-Year-Old Offspring

Noten et al. (2015) examined the effect of hypothyroxinemia during pregnancy on school performance of offspring at 5 years of age. In line with other studies, hypothyroxinemia was defined as an fT4 level less than the 10th percentile of distribution (< 8.06 pmol/L in their sample). Participants were recruited from the Amsterdam Born Children and Their Development study. After exclusion criteria that included mothers who were lost to follow-up or who did not give consent for their child's school test results, 1,196 mother-child pairs were included in the study population. Maternal fT4, TSH, and TPO Ab (> 80 kU/L was considered positive) were measured around the beginning of the second trimester (mean gestational age of 12.9 weeks, interquartile range 11.9-14.3 weeks). School records of offspring were based on scores obtained in arithmetic and language tests from the Central Institute for Test Development, a national monitoring and evaluation system in the

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Netherlands. Multivariable logistic regression was used to assess the effects of fT4 and TSH on the range of poor or subnormal school performance (defined as a rank score below C or B, respectively). Models were adjusted for maternal education, ethnicity, BMI, and depressive symptomatology, as these were related to both the exposure to maternal hypothyroxinemia and outcome of school performance ($p < 0.1$). Maternal age, hypertension, diabetes, smoking, timing of blood sampling, TPO Ab positivity, child gender, gestational age, and birthweight were evaluated as potential confounders, but were found to not be associated with the predictor and outcome and thus not included in the regression analyses. Additional analyses were repeated after excluding pre-term births (< 32 weeks of gestation) or very low birthweight offspring (< 1,500 grams).

The distribution of school test results in terms of rank scores differed between hypothyroxinemic and non- hypothyroxinemic groups, with hypothyroxinemia being associated with lower rank scores in both arithmetic and language tests. Maternal hypothyroxinemia was significantly associated with 1.61-fold (95% CI: 1.05-2.47; $p = 0.03$) increased odds of subnormal arithmetic school performance after adjusting for confounders. However, this association weakened, reaching non-significance, after inverse-probability weighting was applied to account for potential non-response bias. No associations were found with TSH, even before inverse probability weighting. The continuous measure maternal fT4 was inversely associated with the odds of subnormal arithmetic performance, but lost statistical significance after adjusting for confounders. Additional exclusion of pre-term births or very low birthweight offspring did not change these associations.

Key finding: Maternal hypothyroxinemia at the end of the first trimester was associated with reduced arithmetic test performance in 5-year-old offspring. Inverse probability weighting demonstrates that non-response bias may be present in this study, and thus the results should be interpreted with caution.

Detailed Summary of Oken et al. (2009)

Neonatal Thyroxine, Maternal Thyroid Function, and Child Cognition

Oken et al. (2009) examined the relationship between maternal thyroid levels, neonatal thyroid levels, and neurodevelopmental outcomes in childhood. Participants were recruited from a birth cohort and were included in the study if complete information was available on their diet, infant cognition, and T4 levels; women with a history of thyroid problems, pregnancy complications, or other health issues were not excluded from the study. Maternal TSH, total T4, and TPO Ab levels were assayed once during the first trimester (mean 10.2 GW). The researchers did not measure fT4. Neonatal total T4 levels were sampled around 2 days after birth. Children underwent neurodevelopmental testing at 6 months and 3 years. At 6 months, children completed the VRM test, which measures the ability of an infant to recognize visual stimuli and to respond preferentially to novel stimuli. The PPVT and the Wide Range Assessment of Visual Motor Ability (WRAVMA) were administered at 6 years of age. The VRM and PPVT have been found to be good predictors of later intelligence, with levels of predictive validity similar to those of the BSID (Oken et al., 2009). The WRAVMA assesses visual-spatial analysis, visual-motor ability, and fine motor skills. Linear regression models, adjusted for other variables such as gender and age at delivery, were used to investigate the relationship between thyroid hormone levels and neurodevelopmental outcomes, with adjustment for covariates including gestation length, age at testing, sex, maternal education, and ethnicity.

Neonatal total T4 was not associated with either the PPVT or WRAVMA scores. Contrary to expectations, it was associated with lower scores on the VRM test, both as a continuous variable

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(β = -0.5; 95% CI -0.9, -0.2) and as a categorical variable. Maternal thyroid function (as assessed by total T4, TSH, TPO Ab, and history of thyroid disease) was not associated with children's scores on any of the neurodevelopmental outcomes studied. Further maternal and neonatal total T4 were evaluated as opposed to fT4, which is the form of the hormone that is available to cross the placenta and may be a better indicator for an offspring's neurodevelopmental outcome. There was no significant association between maternal total T4 levels and neonatal total T4 levels.

Key Finding: Neonatal total T4 levels within the euthyroid range were not predictive of cognitive outcome, nor were they associated with maternal T4 levels. Maternal thyroid function (T4, TSH, TPO Ab measured at approximately 10 GW) was not associated with any of the neurodevelopmental outcomes assessed. This study did not make an attempt to separately analyze hypothyroxinemic maternal-child pairs.

Detailed Summary of Pop et al. (1999)

Low Maternal Free Thyroxine Concentrations During Early Pregnancy Are Associated with Impaired Psychomotor Development in Infancy

Pop et al. (1999) conducted a prospective cohort study to examine the association between maternal thyroid hormones during early gestation and children's neurodevelopment in an iodine-sufficient region. Women were recruited from a medical center and from community midwife practices at 12 GW. In the 291 healthy women who consented to participate, assessments of maternal thyroid function—fT4, TSH, and TPO Ab levels—were completed at 12 GW and 32 GW. At various stages of follow-up, women were excluded from the study due to neonatal deaths, moving outside of the area, and other pregnancy complications. Children of women remaining in the study at 10 months post-partum (n = 220) completed the Dutch version of the BSID to evaluate mental and psychomotor development using the MDI and PDI, respectively. Pop et al. (1999) conducted t-tests to investigate maternal thyroid levels in the lowest 5th (< 9.8 pmol/L) and 10th (< 10.4 pmol/L) percentiles of fT4 levels at 12 and 32 GW. The authors also performed linear and logistic regression analyses, adjusted for confounders including maternal depression, psychosocial factors, tobacco and alcohol use during pregnancy, and demographic variables. Data analyses were conducted using t-tests, linear regression, and logistic regression.

Children of the 22 women in the lowest 10th percentile of fT4 at 12 GW had significantly lower scores on the PDI than the rest of the children (mean difference: 7.4, 95% CI: 1.1, 13.9). No significant differences were found when investigating PDI scores at 32 GW. MDI scores showed differences associated with fT4 levels, but these failed to reach significance at both 12 and 32 GW. Pop et al. (1999) also found a strong correlation between PDI scores and maternal fT4 levels ($r = 0.46$, $p = 0.03$) (see Figure 8). Although the authors did not present the equation representing the relationship in Figure 8,[15] their Figure 2 was digitized using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Microsoft® Excel on the extracted data. By doing so it was determined that for every 1 pmol/L change in fT4 there is an estimated 8.5 point change in PDI (95% CI: 0.01 - 17.04).[16] Children of mothers with fT4 concentrations in the lowest

[15] EPA attempted to contact study authors on July 20, 2015. To date, no response has been received.

[16] R^2 value based on Excel analysis = 0.18; R^2 value reported by Pop et al. (1999) = 0.21.

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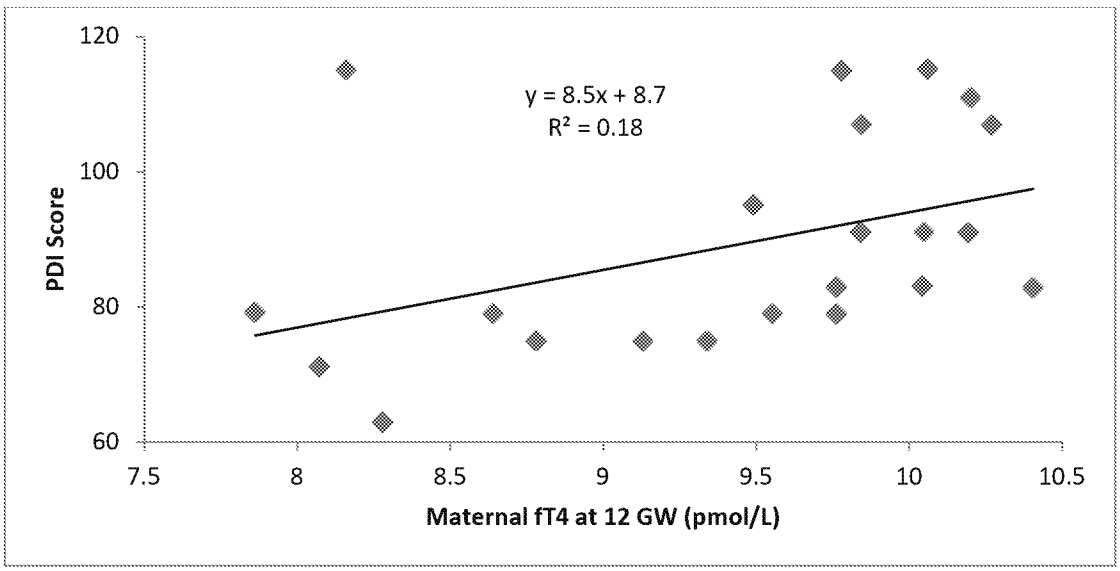
fT4 5th percentile (n = 11) and 10th percentile also had lower scores on the MDI subscale, although these differences were not significant. The results suggest that the timing of hypothyroxinemia during pregnancy may be important as it relates to performance on the BSID.

Pop et al. (1999) additionally performed logistic regression analyses to investigate associations between maternal variables and low PDI scores (defined as below 84 points). In univariate regression analyses, fT4 in the lowest 10th percentile at 12 GW was significantly associated with a low PDI score (relative risk (RR) = 3.6; 95% CI: 1.1-12.1). To control for the effect of possible confounders, Pop et al. (1999) performed a multiple logistic regression analysis that included a host of additional pregnancy-related factors, maternal mood indicators, and demographic features. The relative risk estimate for the association between fT4 in the lowest 10th percentile at 12 GW and low PDI scores increased (RR = 5.8; 95% CI: 1.3-12.6) in the multivariate regression analysis. No significant associations were found in univariate or multivariate regression analyses between fT4 in the lowest 10th percentile at 32 GW and low PDI scores.

Figure 8. Digitization of Figure 2 from Pop et al. (1999): Correlation between PDI Score and fT4 at 12 GW for Women in the Lowest 10th Percentile of fT4



***Key finding*:** Maternal fT4 levels in the lowest 10th percentile in the first trimester among an iodine-sufficient population were significantly associated with reduced psychomotor development in 10-month-old infants (a drop in the PDI score of 8.5 points was associated with every 1 pmol/L reduction in fT4).

Detailed Summary of Pop et al. (2003)

Maternal Hypothyroxinemia during Early Pregnancy and Subsequent Child Development: A 3-Year Follow-Up Study

In a prospective 3-year study, Pop et al. (2003) measured thyroid hormone levels (TSH and fT4) in randomly selected pregnant women at 12, 24, and 32 gestational weeks in the Netherlands. Pop et al. initially approached 1,361 women to join their cohort. Eight of these women were excluded due to the presence of hyper- or hypothyroidism. From the remaining 1,353 women, Pop et al. (2003) recruited 135 hypothyroxinemic cases (fT4 levels in the lowest 10th percentile (< 12.4 pmol/L)) and matched

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them based on parity and gravidity with an equal number of controls (fT4 levels in the 50th-90th percentiles (15.6–19.1 pmol/L)). TSH, fT4, and TPO Ab were assessed at 12 GW. At various stages of follow-up, women were excluded from the cohort due to a variety of exclusion criteria such as subclinical thyroid dysfunction (high TSH, normal fT4), fertility problems, autoimmune diseases, obstetrical complications, major depressive episodes, and prolonged or repeated hospitalizations after birth. This resulted in 63 cases and 62 controls at the age of 1 year and 57 cases and 58 controls at the age of 2 years. (For complete details on inclusion and exclusion of women in the cohort, see Figure 1 of Pop et al., 2003).

Infant development was assessed at 1 and 2 years of age using the Dutch version of the Bayley Scales of Infant Development to evaluate MDI and PDI scores. The mean scores for cases and controls are presented in Table 20. This table demonstrates that statistically significant differences in MDI and PDI existed between the cases and controls at both 1 and 2 years of age.

Table 20. Differences on Bayley Mental (MDI) and Motor (PDI) Subscales Assessed at 1 and 2 Years[a]

	Cases[b]	Controls[c]	*p*-value	95% CI
One Year				
Mental, mean (SD)	95 (15)	105 (14)	0.004	4-16
Motor, mean (SD)	91 (15)	99 (14)	0.02	3-12
Two Years				
Mental, mean (SD)	98 (15)	106 (14)	0.02	4-12
Motor, mean (SD)	92 (16)	102 (16)	0.005	6-16

Source: Pop et al. (2003, Table 2).
[a] Based on a two-tailed t-test.
[b] fT4 levels in the lowest 10th percentile (< 12.4 pmol/L).
[c] fT4 levels in the 50th-90th percentiles (15.6– 19.1 pmol/L)

Pop et al. (2003) also evaluated the relationship between maternal fT4 levels at 12 GW with MDI and PDI at 2 years of age. They determined that there was a significant correlation between maternal fT4 levels at 12 gestational weeks and both MDI and PDI scores (MDI: r = 0.48, $p = 0.001$; PDI: r = 0.38, $p = 0.006$) (see Figure 9) among the women with hypothyroxinemia. Although Pop et al. (2003) did not present the equation representing the relationship in Figure 9, their Figure 3 was digitized using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Excel on the extracted data.[17] By doing so, it was determined that for every 1 pmol/L change in fT4 there is an estimated 8.4 point change in PDI (95% CI: 4.0–12.8)[18] and 6.3 point change in MDI (95% CI: 1.92–10.62).[19] Analogous analyses were not presented for individuals assessed at 1 year of age or for controls.

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17 EPA attempted to contact study authors on July 20, 2015. To date, no response has been received.

18 R^2 value based on Excel analysis = 0.22; R^2 value reported by Pop et al. (2003) = 0.23.

19 R^2 value based on Excel analysis and reported by Pop et al. (2003) = 0.13.

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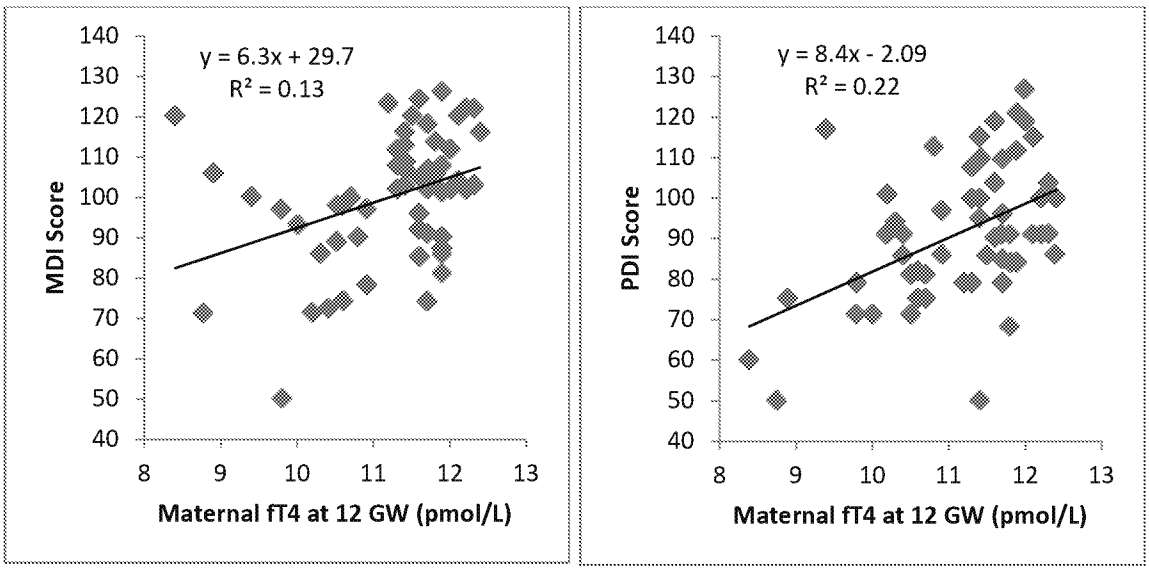
In addition, Pop et al. (2003) examined the pattern of maternal fT4 levels throughout pregnancy and the distribution of Bayley Scale scores in the cases and controls. The authors found that the lowest Bayley scores were associated with the offspring of first-trimester hypothyroxinemic women (cases) whose fT4 levels continued to decrease as pregnancy progressed. Other women who started out as hypothyroxinemic, but experienced increases in fT4 levels in either the second or third trimesters had children with similar MDI and PDI scores to women who were not hypothyroxinemic in the first trimester. Additionally, the authors noted that children of women who had fT4 in the 50th to 90th percentile range during the first trimester (controls), but later experienced a drop in fT4 did not exhibit an association between neurodevelopment and fT4.

Figure 9. Digitization of Figure 3 from Pop et al. (2003): Linear Regression of Maternal fT4 Concentrations of Cases with fT4 in the Lowest 10th Percentile at 12 GW with MDI and PDI Scores at 2 Years of Age



Pop et al. (2003) noted several potential shortcomings of their analysis. One is that the subgroups they assessed when evaluating the impact of the pattern of fT4 on PDI and MDI became very small because they excluded cases with potentially confounding data (e.g., mothers with episodes of depression). This may be why a statistical analysis of the individuals just in the group with low fT4 throughout pregnancy was not included in Pop et al. (2003). Further, Pop et al. (2003) noted that an assessment of a child's abilities at a very young age (i.e., less than 1 year of age) may have limited value once the child reaches school. However, Bayley scores at 2 years of age have been found capable of predicting a child's ability at 5 years, particularly if the child is at risk of developmental delays (Van Baar & De Graff, 1994 as cited by Pop et al., 2003; also see Appendix F). Additionally, no data on daily food or iodine intake in the population are available. The authors point out that previous studies in the same general population have reported sufficient iodine intake. However, according to the study authors, the sufficiency of this iodine intake specifically for pregnant women has been called into question (see van Rees-Wortelboer, Schröder-van der Elst, Lycklama, & Van der Heide, 1987; Brussaard et al., 1997; Morreale de Escobar & Escobar del Rey, 1999; Utiger, 1999, as cited by Pop et al., 2003). Lastly, Pop et al. (2003) note that the trend in norms for the developmental tests are representative of the general population, since the mean MDI and PDI of controls in this study are similar to those reported in their prior 1999 study.

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The Pop et al. (2003) results indicate that hypothyroxinemia in the first trimester is associated with impaired mental and psychomotor development in childhood and that this relationship is likely to be even more pronounced in individuals with low fT4 throughout the entire course of pregnancy. Additionally, it should be noted that the relationship found between fT4 and PDI is essentially the same (i.e., for each pmol/L change in fT4 there is a resulting 8.4 point change in PDI) as that found by Pop et al. (1999).

Key finding: Maternal fT4 levels in the lowest 10th percentile in the first trimester were significantly associated with a clinically relevant difference in psychomotor and mental development among 2-year-olds (a drop in the PDI score of 8.4 points and in the MDI score of 6.3 points was associated with every 1 pmol/L reduction in fT4).

Detailed Summary of Román et al. (2013)

Association of Gestational Maternal Hypothyroxinemia and Increased Autism Risk

Román et al. (2013) conducted a study to examine the role of maternal hypothyroxinemia in autistic symptoms in children at 6 years of age. Participants were recruited from a population-based cohort in the Netherlands and included in the study given complete biomarker and assessment data. Maternal TSH, fT4, and TPO Ab were measured near the beginning of the second trimester at a mean of 13.4 GW. Autistic symptoms were assessed via two questionnaires administered to parents: the Pervasive Developmental Problems Scale (PDP) and the Social Responsiveness Scale (SRS). The PDP is a subscale of the Child Behavior Checklist for Toddlers, which is an assessment of problem behaviors in children that is typically completed by parents or caregivers. The PDP measures autistic symptoms and has good predictive validity for identifying preschoolers at risk of autism spectrum disorder. The SRS is based on parent observations of social, language, and repetitive behaviors in a natural setting. Román et al. (2013) analyzed associations between maternal TSH and fT4 levels and PDP and SRS variables using linear and logistic regression models. Maternal fT4 levels were analyzed as a continuous variable (divided by the SD to facilitate interpretation) and categorically using definitions of mild and severe hypothyroxinemia (< 10th and 5th percentile of the sample, respectively). Children with borderline and clinical behavioral problems were defined as those above the 93rd and 98th percentiles on the PDP, respectively. A probable autistic child was defined by a PDP score > 98th percentile and an SRS score in the top 5% of the sample. Regression models were adjusted for confounders including sex, ethnicity, gestation age, birthweight, parental age, education, smoking history, and intelligence. In the linear regression analysis PDP and SRS scores were square root-transformed to satisfy the normality assumption.

Román et al. (2013) found no associations between the continuous measures of maternal TSH and fT4 per SD and children's borderline or clinical behavioral problems. However, the authors found that severe maternal hypothyroxinemia was associated with almost four-fold increased odds of having a probable autistic child (OR_{adj} = 3.89, 95% CI = 1.83, 8.20). Based on linear regression analysis, severe maternal hypothyroxinemia was also associated with a higher score of child autistic symptoms based on the PDP (β = 0.23, 95% CI = 0.07, 0.37) and SRS (β = 0.05, 95% CI = 0.01, 0.10) scales. However, the authors did not find this relationship to be concentration dependent. This is demonstrated by the negative associations seen between fT4 per SD and only mild hypothyroxinemia and the outcomes of lower PDP and SRS scale scores, as shown in Table 21. It is unknown if there is a concentration-dependent relationship between fT4 and scores on the PDP or SRS scale (or risk of

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autism) when considering only individuals with severe hypothyroxinemia, because this analysis was not conducted. No increased risk of autism was found for children of mothers positive for TPO Ab.

Table 21. Summary of Key Findings from Román et al. (2013)

Variable	Pervasive Developmental Problems (PDP) β (95% CI), *P*	Social Responsiveness Scale (SRS) β (95% CI), *P*
TSH per SD	0.01 (-0.02, 0.03), 0.68	0.01 (-0.001, 0.01), 0.12
fT4 per SD	-0.03 (-0.06, -0.01), 0.04	-0.002 (-0.01, 0.01), 0.67
Mild hypothyroxinemia	0.09 (-0.02, 0.19), 0.62	0.02 (-0.01, 0.04), 0.33
Only mild hypothyroxinemia	-0.04 (-0.17, 0.004)	-0.02 (-0.06, 0.02), 0.28
Severe hypothyroxinemia	0.23 (0.07, 0.37), 0.04	0.05 (0.01, 0.10), 0.01

Source: Román et al. (2013, Table 3).
Notes: Mild hypothyroxinemia (n = 136): 0.03 < TSH < 2.5 mIU/L and fT_4 < 11.82.
Only mild hypothyroxinemia (n = 295): 0.03 < TSH < 2.5 mIU/L and 10.99 < fT_4 < 11.82.
Severe hypothyroxinemia (n = 159): 0.03 < TSH < 2.5 mIU/L and fT_4 < 10.99 pmol/L.
The β's are not interpretable, as the mathematically transformed scores were used in the analysis.

Key finding: Severe maternal hypothyroxinemia at a mean gestational age of 13.4 weeks was significantly associated with an almost four-fold increased risk of being a probable autistic child and a higher score on a scale of autistic symptoms among 6-year-old children.

Detailed Summary of Velasco et al. (2009)

Effect of Iodine Prophylaxis during Pregnancy on Neurocognitive Development of Children during the First Two Years of Life

Velasco et al. (2009) conducted an intervention study among pregnant women in southern Spain to evaluate the relationship between iodine supplementation and child neurodevelopment. Participants were recruited from a medical center and excluded if they had any history of thyroid disease. A supplement dose of 300 µg/day of iodine as potassium iodine (KI) was given to 133 women during the first trimester of pregnancy. The majority of these women (76.9%) started taking the supplements before the 10th week of pregnancy. The control group consisted of 61 women who visited the medical center during their last month of pregnancy and who did not receive iodine supplements. Thyroid hormones (TSH, fT3, fT4), thyroglobulin, and urinary iodide concentrations were measured in each trimester in the KI supplement group and in the last trimester for the control group. TPO Ab were not measured in this study.

The authors evaluated children between the ages of 3 and 18 months using the Bayley Scales of Infant Development for mental, psychomotor, and behavior scores. The researchers assessed associations between maternal thyroid levels and children's neurodevelopment using multivariate logistic regression. Urinary iodide levels in the third trimester were significantly higher in the KI supplement group than in the controls. Among the women receiving iodine supplements, urinary iodide concentrations were 263 µg/L (SD = 121) in the third trimester, as compared to 153 µg/L (SD = 110) in the first trimester. When comparing children's scores on the MDI, no significant differences between groups were found. However, PDI scores were significantly greater in the children whose mothers had received KI supplements (p = 0.02). Additionally, the PDI among these children

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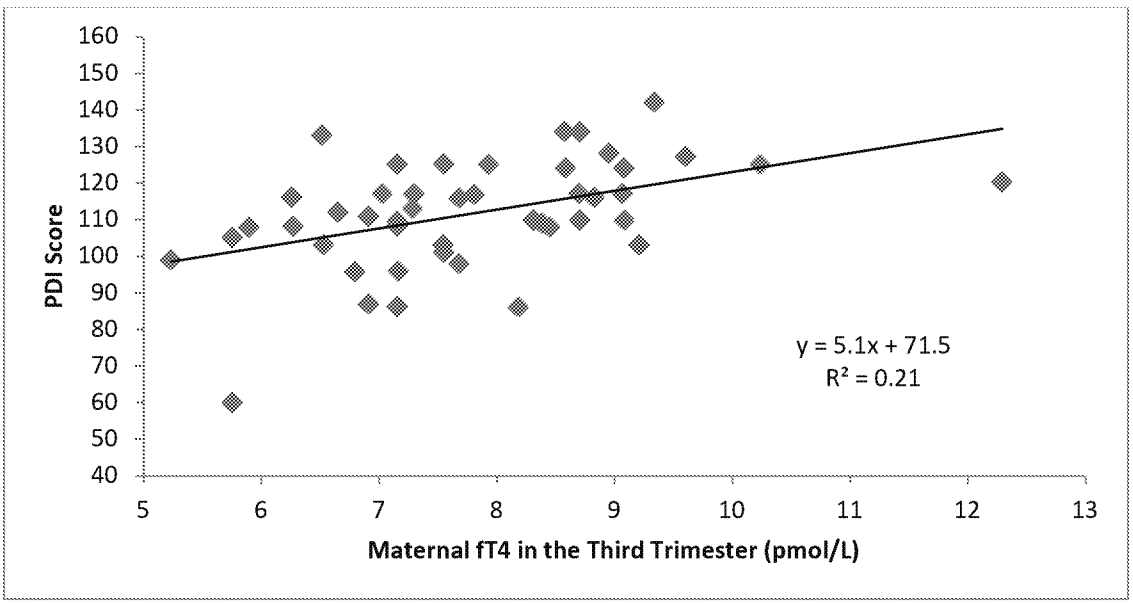
correlated significantly with the fT4 levels during the third trimester (r = 0.50, $p < 0.0001$). Although Velasco et al. (2009) did not present the equation representing the relationship in Figure 10,[20] Figure 1 in the study was digitized using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Excel on the extracted data. By doing so it was determined that for every 1 pmol/L change in fT4 there is an estimated 5.1 point change in PDI (95% CI: 2.11-8.18).[21] The same relationship was not found in the children of mothers who did not receive iodine supplements.

It is important to note that, contrary to expectations, the group that received the KI supplements had a lower mean maternal fT4 level than the group that did not receive supplements. This, in addition to the fact that the control group of women who did not receive KI supplements had less than half as many members, may help explain the lack of findings relating fT4 to PDI in the non-KI supplemented group. A possible explanation for these unexpected findings in the supplemented group is that high iodine can be toxic to the thyroid (Leung & Braverman, 2014). The supplemented group was above the WHO recommended dietary allowance for iodine in pregnancy (250 µg/day) (Zimmermann & Delange, 2004), especially if this population already had dietary sources of iodine.

Figure 10. Digitization of Figure 1 from Velasco et al. (2009): Correlation between fT4 in the Third Trimester (KI Supplement Group) and PDI



While the focus of Velasco et al. (2009) is on the impact of iodine supplementation during pregnancy and neurocognitive development, the results also support the notion that there is an association between fT4 levels during pregnancy and future neurodevelopment in children. The findings are particularly relevant to populations with sufficient levels of iodine intake.

Key finding: Among a group of women with sufficient iodine intake through iodine supplementation, fT4 levels in the third trimester correlated significantly with psychomotor development in infants

[20] EPA attempted to contact study authors on July 20, 2015. To date, no response has been received.

[21] R^2 value based on Excel analysis = 0.21; R^2 value reported by Velasco et al. (2009) = 0.25.

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aged 3 to 18 months (a drop in the PDI score of 5.1 points was associated with every 1 pmol/L reduction in fT4).

Detailed Summary of Vermiglio et al. (2004)

Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild–Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries

Vermiglio et al. (2004) aimed to investigate the association between iodine deficiency-related maternal hypothyroxinemia and cognitive and behavioral deficits in children. The researchers conducted a 10-year prospective study in Northern Sicily on children born to healthy women from a moderately iodine-deficient area (n = 16) and controls from a marginally iodine-sufficient area (n = 11). The authors did not provide details on participant recruitment. Maternal levels of thyroid hormones (T3, T4, fT3, fT4, TSH, and T4-binding globulin) were assessed during the first and second trimesters at approximately 8, 13, and 20 weeks of gestation. TPO Abs were measured, but not discussed in the subsequent analysis. Hypothyroxinemia was defined as low fT4 values compared to a group of 50 healthy women with moderately adequate iodine intake. Children underwent neurological observations and testing (e.g., assessments of fine motor coordination, speech, and language) at ages 18 to 36 months. At ages 8 to 10 years, the authors administered questionnaires to parents and teachers to assess ADHD based on symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders*. In addition, intelligence was measured using the WISC-III. Thyroid levels in children were assessed at birth, ages 18 to 36 months, and ages 8 to 10 years. Vermiglio et al. (2004) analyzed data by comparing mean differences between the two areas and performing linear regressions.

Children's thyroid levels were found to be within normal limits at all time points studied. Questionnaires indicated the presence of ADHD in 11 of the 16 children from the moderately iodine-deficient area, but in none of the 11 control children. Additionally, the mean IQ score was 18 points lower in the iodine-deficient area than in the iodine-sufficient area (92.1 ± 7.8 vs. 110 ± 10, $p < 0.00005$). Furthermore, when all of the children (from both the moderately iodine-deficient area and the iodine-sufficient area) were grouped together, a strong correlation was observed between a child's IQ score and maternal fT4 at week 20 ($r = 0.56$, $p < 0.005$) (see Figure 11), as well as between a child's IQ score and TSH ($r = -0.63$, $p < 0.001$). Although Vermiglio et al. (2004) did not present the equation representing the relationship in Figure 11,[22] their Figure 3 was digitized using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Excel on the extracted data. By doing so, it was determined that for every 1 pmol/L change in fT4 there is an estimated 2.6 point change in IQ (95% CI: 0.90-4.34).[23] Vermiglio et al. (2004) did not present analyses of the relationship between maternal fT4 at 8 or 13 GW and children's IQ.

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[22] EPA attempted to contact study authors on July 20, 2015. To date, no response has been received.

[23] R^2 value based on Excel analysis = 0.29; R^2 value reported by Vermiglio et al. (2004) = 0.31.

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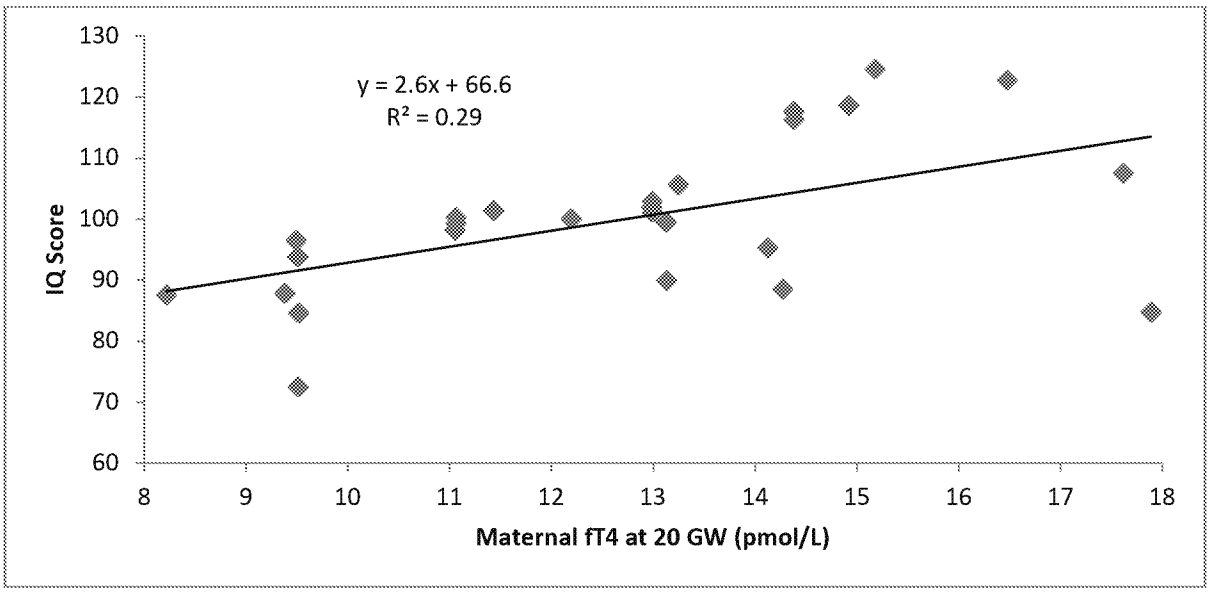
Figure 11. Digitization of Figure 3 from Vermiglio et al. (2004): Linear Regression between IQ of Both Groups and fT4 Levels at 20 GW (Converted from ng/dL to pmol/L)



Key finding: There was a quantifiable relationship between fT4 at GW 20 and IQ at 8 to 10 years of age (a drop in IQ of 2.6 points was associated with every 1 pmol/L reduction in fT4).

5.3.3 Results of Step 3

After identifying 15 Group 1 studies, EPA focused on five studies that could be used to describe how increments changes in thyroid hormone levels in early pregnancy and result in subsequent changes in neurodevelopment.

Group 1 Studies Not Evaluated Further

As described in Table 22, the Group 1 studies Chevrier et al. (2011), Ghassabian et al. (2014), Gyllenberg et al. (2016), Henrichs et al. (2010), Modesto et al. (2015), Moleti et al. (2016), Noten et al. (2015), Oken et al. (2009), Román et al. (2013) and Velasco et al. (2009) did not meet the criteria for the planned analysis to describe the relationship between a continuous measure of fT4 and neurodevelopment. Six of the studies which are not further analyzed (Gyllenberg et al., 2016; Ghassabian et al., 2014; Modesto et al., 2015; Moleti et al., 2016; Noten et al., 2015; Oken et al., 2009), were not further evaluated given they did not have statistically significant results for their continuous measures of fT4 which is inclusive of the entire range of fT4 in the study. However, it is noteworthy that of these six studies, four also conducted categorical analyses evaluating if hypothyroxinemia was associated with adverse neurodevelopmental outcomes (Gyllenberg et al., 2016; Ghassabian et al., 2014; Modesto et al., 2015; Noten et al., 2015). Three of them found a statistically significant association (Gyllenberg et al., 2016; Ghassabian et al., 2014; Modesto et al., 2015). The only study that did not find a statistically significant association was Noten et al. (2015). The authors initially found an association between maternal hypothyroxinemia and reduced performance in an arithmetic test, however, after inverse probability weighting, this association diminished to borderline significant and the author's suggest caution in the interpretation of their results due to possible non-response bias. A summary of each of these studies results along with EPA's Evaluation of the paper is presented in Table 22.

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Additional discussion on the association between maternal hypothyroxinemia and adverse neurodevelopmental outcomes is presented in Section 5.4.

Group 1 Studies Considered for Further Analysis

Five studies in this group of fifteen Group 1 studies were identified (Pop et al., 1999, 2003; Finken et al., 2013; Korevaar et al., 2016; and Vermiglio et al., 2004) that included data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment. 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. These studies can be identified in the "EPA Evaluation Column" of Table 22 which states further analysis was conducted.

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Table 22. Summary of Group 1 Study Results Based on Continuous Measure of fT4

Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Chevrier et al. (2011)	287 mother-child pairs (88% Mexican) from Salinas Valley, CA	No specific data on iodine status provided.	One time during pregnancy (mean: 26.9 GW ± 3.4 GW) (ng/dL)	Performance IQ Age 5 yr	-4.12 (-13.73, 5.49)[a]	Results of the analysis did not find a significant relationship between maternal thyroid hormone levels during late second trimester of pregnancy and performance on IQ tests or psychomotor and metal development.	*Further analysis was not performed* because the relationship between fT4 and neurodevelopment was evaluated late in pregnancy (i.e. after 20 gestational weeks) and did not reach statistical significance.
				Bayley Scale score MDI			
				Age 6 mo	-3.14 (-7.65, 1.36)		
				Age 1 yr	-0.48 (-6.22, 5.26)		
				Age 2 yr	-4.29 (-11.60, 3.02)		
				Bayley Scale score PDI			
				Age 6 mo	-3.27 (-9.63, 2.82)		
				Age 1 yr	-6.40 (-13.89, 1.08)		
				Age 2 yr	-2.67 (-8.95, 3.62)		
				Other endpoints Age 5 yr			
				Motor Development			
				WRAVMA			
				-Pegboard– Dominant	-3.76 (-15.45, 7.93)		
				-Pegboard–Nondominant	-4.21 (-16.03, 7.61)		
				McCarthy			
				-Draw-a-child	-5.98 (-16.74, 4.77)		
				-Gross Motor-Leg	-0.14 (-1.60, 1.32)		
				Gross Motor- Arm	0.08 (-1.51, 1.66)		
				Language Development			
				-WPPSI Vocabulary	-0.21 (-1.98, 1.57)		
				-PPVT	-2.71 (-14.18, 8.77)		
				Memory			
				McCarthy			
				-Words and Sentences	0.10 (-11.32, 11.52)		
				-Digit Span Forward	4.06 (-4.72, 12.83)		
				-Digit Span Backward	4.43 (-2.55, 11.42)		

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
				School Readiness			
				Woodcock-Johnson/Munoz			
				-Letter-Word	-1.86 (-9.33, 5.60)		
				-Applied Problems	-3.82 (-14.06, 6.42)		
				Attention			
				CBCL			
				-ADHD	-0.10 (-2.03, 1.82)		
				KCPT			
				-ADHD Conf. Index	7.52 (-4.86, 19.91)		

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Finken et al. (2013)	1,765 Dutch mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (median:12.9 GW, interquartile range (IQR): 11.9–14.3) (pmol/L)	Age 5-6 yr Baseline Speed Mean reaction time, milliseconds **Reaction time, SD, milliseconds** Pursuit Deviation, millimeters SD of deviation, millimeters Tracking Mean distance, millimeters Accuracy stability, millimeters Movement speed, seconds	 -4.5 (-9.0, 0.1)[b] **-4.9 (-9.5, -0.2)** -0.01 (-0.22, 0.21) 0 (-0.20, 0.21) -0.01 (-0.11, 0.09) 0.04 (-0.06, 0.15) -0.08 (-0.34, 0.18)	Continuous maternal fT4 levels at a median of 12.9 weeks were inversely associated with the reaction time variability among 5- to 6-year-old children (an increase in the reaction time SD of 4.9 ms was associated with every 1 pmol/L reduction in maternal fT4). Considering fT4 as a categorical variable demonstrated that there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time, when comparing the offspring of hypothyroxinemic to non-hypothyroxinemic mothers.	*Further analysis was performed* to estimate the incremental impact doses of perchlorate (using the BBDR model) have on the standard deviation of reaction time

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Gyllenberg et al. (2016)	1,010 Finnish mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (2-4 months pregnancy) (pmol/L)	Odds of diagnosis of schizophrenia/ schizoaffective disorder *Log-Transformed fT4 During Early Gestation* Unadjusted Individually adjusted for maternal psychiatric history Individually adjusted for province of birth Individually adjusted for maternal smoking during early gestation Adjusted for maternal psychiatric history, province of birth, and maternal smoking	Various Ages[c] **0.54 (0.31, 0.94)** **0.53 (0.30, 0.94)** **0.57 (0.33, 0.999)** 0.71 (0.39, 1.27) 0.74 (0.40, 1.38)	An association between fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range) and odds of schizophrenia diagnosis was found using conditional logistic regression. However, this relationship was attenuated after controlling for smoking. Considering fT4 as a categorical variable demonstrated that 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.	*Further analysis was not performed.* While the relationship between maternal fT4 as a continuous variable and odds of offspring schizophrenia diagnosis was observed, statistical significance was lost after adjustment for confounders.

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Ghassabian et al. (2014)	3,727 Dutch mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (mean: 13.5 GW ± 2 GW, range: 5.7-17.9 GW) (pmol/L)	Nonverbal IQ at 6 years	-0.24 (-0.61, 0.14), fT4 per SD[d]	Maternal hypothyroxinemia during early pregnancy (mean GW = 13.5) was associated with an average reduction of 4.3 points (p = 0.001, 95% CI: -6.68, -1.81) in children's nonverbal IQ at age 6. Continuous measures of maternal thyroid function (TSH, fT4) across the entire range (not the hypothyroxinemic range) and subclinical hypothyroidism were not significantly associated with nonverbal IQ in 6-year-old children.	*Further analysis was not performed* because no relationship was found between a continuous measure of maternal fT4 and neurodevelopment.
Henrichs et al. (2010)	2,779 Dutch mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (mean: 13.3 GW ± 1.7 GW) (pmol/L)	Odds of expressive language delay at 18 and 30 months[e] Expressive Language Delay 18 mo 30 mo 18 and 30 mo Nonverbal cognitive delay 30 mo	*Odds Ratio (OR)*[f] 0.95 (0.83, 1.09), fT4 per SD **0.84 (0.71, 0.99), fT4 per SD** 0.90 (0.80-1.01), fT4 per SD 0.85 (0.72, 1.01), fT4 per SD	Severe maternal hypothyroxinemia was associated with expressive language delay at 18 and 30 months and non-cognitive delay at 30 months. Further, there was an increase in the odds of expressive language delay and	*Further analysis was not performed* because the SD needed to translate this result for a regression analysis was not available.

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
						non-cognitive delay when comparing the offspring of children exposed to mild versus severe maternal hypothyroxinemia, suggesting a potential dose-response between the severity of hypothyroxinemia and expressive language delay and non-cognitive delay. Additionally, maternal fT4 levels per SD were associated with a reduction in odds of expressive language delay at 30 months (OR = 0.84 per SD of fT4).	
Korevaar et al. (2016)	3,839 Dutch mother-child pairs	Yes, urine samples were taken for a random subset of the population (n = 672)	One time in pregnant mother (median: 13.2, GW; range 9-18 GW) (pmol/L)	Child IQ at 6 years[g]	Variable: β (SE) fT4: 33.81 (12.25) fT4[2]: -6.235 (2.210)	The authors concluded that both low and high maternal fT4 concentrations during pregnancy were associated with statistically significant lower child IQ and lower gray matter and cortex volume.	*Further analysis was performed* to estimate the incremental impact doses of perchlorate (using the BBDR model) have on the IQ.

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Modesto et al. (2015)	127 Dutch mother-child pairs	No specific data on iodine status provided.	One time in pregnant mother (mean: 13.6 GW; range 6.6-17.9) (result presented is specific to mothers with TH taken < 13 GW) (ng/dL)	Parent-reported ADHD index scores of offspring at 8 years *Parent Reported ADHDi Score* fT4 Level per SD -Unadjusted -Adjusted for age and sex -Fully adjusted model[h] fT4 per SD (gestational age < 13 weeks -Unadjusted -Adjusted for age and sex -Fully adjusted model[h]	 -0.01 (-0.02, 0.01) -0.004 (-0.02, 0.01) -0.01 (-0.02, 0.01) **-0.02 (-0.04, -0.004)** **-0.02 (-0.04, -0.001)** -0.02 (-0.03, 0.003)	Maternal hypothyroxinemia in early pregnancy was associated with higher ADHDi scores in 8-year-old children compared with non-exposed children, after adjusting for confounders (7% increase in ADHDi scores (95% CI: 3%-15%)). When considering fT4 as a continuous variable, the association between maternal fT4 and offspring ADHDi scores was attenuated with the adjustment of confounders.	*Further analysis was not performed* because no relationship was found between a continuous measure of maternal fT4 and neurodevelopment.

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Moleti et al. (2016)	59 Sicilian mother-child pairs	Yes, urinary iodide excretion measured in random urine samples throughout gestation and from children at time of cognitive evaluation.	Every 6-weeks, from < 12 GW to term (pmol/L)	Child IQ at 6-12 years	fT4 measured ≤ 12 GW 1.192 (0.980, 1.450) [exp β Verbal IQ] 1.053 (0.881, 1.259) [exp β Performance IQ]] 1.103 (0.928, 1.311) [exp β Full Scale IQ] fT4 measured 13-18 GW 1.217 (1.015 -1.459) [exp β Verbal IQ] 1.010 (0.855 -1.194) [exp β Performance IQ]] 1.165 (0.980-1.385) [exp β Full Scale IQ] fT4 measured 19-24 GW 1.234 (0.991-1.537) [exp β Verbal IQ] 1.125 (0.897-1.411) [exp β Performance IQ] 1.155 (0.937-1.425) [exp β Full Scale IQ] fT4 measured 25-30 GW 1.137 (0.928-1.393) [exp β Verbal IQ] 1.003 (0.810-1.243) [exp β Performance IQ] 1.031 (0.847-1.254) [exp β Full Scale IQ] fT4 measured GW 31-term 1.191 (0.982-1.445) [exp β Verbal IQ]	The authors found that maternal iodine status is predictive of neurodevelopmental outcomes in offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and FSIQ, but failed to reach statistical significance.	*Further analysis was not performed* because the relationship between fT4 and neurodevelopment did not reach statistical significance.

ED_005043_00079783-00102

Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
					1.010 (0.834-1.224) [exp β Performance IQ] 1.070 (0.895-1.280) [exp β Full Scale IQ]		
Noten et al. (2015)	1,196 Dutch mother-child pairs	No specific data on iodine status provided.	One time in pregnant mother, (mean: 12.9 GW; range 11.9-14.3) (pmol/L)	Odds of poor school performance at 5 years Arithmetic Test Poor school performance fT4, continuous -Unadjusted -Adjusted[j] Arithmetic Test Subnormal school performance fT4, continuous -Unadjusted -Adjusted[j] Language Test Poor school performance fT4, continuous -Unadjusted -Adjusted[j] Language Test Subnormal school performance fT4, continuous -Unadjusted -Adjusted[j]	Odds Ratio 0.88 (0.77, 1.02) 0.92 (0.80, 1.07) **0.89 (0.81, 0.98)** 0.92 (0.83, 1.02) 0.95 (0.84, 1.08) 1.02 (0.90, 1.16) 0.98 (0.90, 1.08) 1.02 (0.93, 1.13)	Maternal hypothyroxinemia at the end of the first trimester was associated with reduced arithmetic test performance in 5-year-old offspring. Inverse probability weighting demonstrates that non-response bias may be present in this study, and thus the authors caution that the results should be interpreted with caution.	*Further analysis was not performed.* While the relationship between maternal fT4 as a continuous variable and odds of subnormal arithmetic performance was observed, statistical significance was lost after adjustment for confounders.

ED_005043_00079783-00103

Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Oken et al. (2009)	500 mother-child pairs in Massachusetts	No specific data on iodine status provided.	One time in pregnant mother (mean: 10.2 GW) (Total T4: µg/dL)	Age 6 mo Visual Recognition Memory Peabody Picture Vocabulary Test Wide Range Assessment of Visual Motor Ability	 -0.04 (-0.8, 0.7) [T4][k] -0.1 (-0.7, 0.5) [T4][k] 0.004 (-0.6, 0.6) [T4][k]	Neonatal total T4 levels within the euthyroid range were not predictive of cognitive outcome, nor were they associated with maternal T4 levels. Maternal thyroid function (T4, TSH, TPO Ab measured at approximately 10 GW) was not associated with any of the neurodevelopmental outcomes assessed. This study did not make an attempt to separately analyze hypothyroxinemic maternal-child pairs.	*Further analysis was not performed* because a relationship between maternal T4 and cognitive outcomes was not found. The study only evaluated maternal T4 and cognitive outcomes (i.e., fT4 was not evaluated).
Pop et al. (1999)	22 children of Dutch women with fT4 < 10th percentile from iodine-sufficient area	No specific data on iodine status provided.	First and third trimesters of pregnancy (result presented is specific to first trimester (12 GW) of pregnancy) (pmol/L)	Bayley Scale score (PDI) at 10 months Bayley Scale score (MDI) at 10 months	**8.5 (0.01, 17.04)**[l,m] Not reported	Maternal fT4 levels in the lowest 10th percentile in the first trimester among an iodine-sufficient population were significantly associated with reduced psychomotor development in 10-month-old infants.	*Further analysis was performed* to estimate the incremental impact doses of perchlorate (using the BBDR model) have on PDI.

ED_005043_00079783-00104

Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Pop et al. (2003)	57 children (2 years old) of Dutch women with hypothyroxinemia	No specific data on iodine status provided.	Repeated each trimester of pregnancy (result presented is specific to first trimester (12 GW) of pregnancy) (pmol/L)	Bayley Scale score (PDI) at Age 2 yr. Bayley Scale score (MDI) at Age 2 yr.	**8.4 (4.0, 12.8)**[l] **6.3 (1.9, 10.62)**	Maternal fT4 levels in the lowest 10th percentile in the first trimester were significantly associated with a clinically relevant difference in psychomotor and mental development among 2-year-olds.	*Further analysis was performed* to estimate the incremental impact doses of perchlorate (using the BBDR model) have on PDI and MDI
Román et al. (2013)	4,039 children of mothers in the Netherlands	No specific data on iodine status provided.	One time during pregnancy (mean: 13.4 weeks) (pmol/L)	Age 6 yr *Pervasive Developmental Problems* Borderline fT4 per SD Clinical fT4 per SD *Autistic Symptoms* Pervasive Developmental Problems fT4 per SD Social Responsiveness Scale fT4 per SD	 0.93 (0.80, 1.09)[n] 0.95 (0.77, 1.17)[n] **-0.03 (-0.06, -0.01)**[n] -0.002 (-0.01, 0.01)[n]	Severe maternal hypothyroxinemia at a mean gestational age of 13.4 weeks was significantly associated with an almost four-fold increased risk of being a probable autistic child and a higher score on a scale of autistic symptoms among 6-year-old children.	*Further analysis was not performed* because the authors cautioned that the betas relating the continuous measure of maternal fT4 and PDP or SRS scale scores were not interpretable because mathematically transformed scores were used in the analyses and the SD needed for analysis was not provided.

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Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation
Velasco et al. (2009)	133 Spanish women who took 300 µg/day potassium iodide from the first trimester	Yes, urinary iodide excretion measured in each trimester of pregnancy.	Repeated each trimester of pregnancy (result presented is specific to third trimester of pregnancy) (pmol/L)	Bayley Scale score (Psychomotor Development Index (PDI)) at 6 months Bayley Scale score (Mental Development Index (MDI)) at 6 months	**5.1 (2.1, 8.2)**[l] 0.3 (CI: NR)	Among a group of women with sufficient iodine intake through iodine supplementation, fT4 levels in the third trimester correlated significantly with psychomotor development in infants aged 3 to 18 months.	*Further analysis was not performed* because the relationship between fT4 and neurodevelopment was evaluated late in pregnancy (i.e. not 1st trimester).
Vermiglio et al. (2004)[o]	27 Italian mother-child pairs (16 iodine-deficient and 11 iodine-sufficient)	Yes, urinary iodide excretion measured in mothers residing in iodine-deficient and iodine-sufficient areas.	Three samples during pregnancy (2 during first trimester, 1 during second trimester; result presented is specific to the second trimester (20 GW) of pregnancy) (pmol/L)	WISC-III total IQ at 8-10 years	**2.6 (0.90, 4.33)**[l]	There was a quantifiable relationship between fT4 at GW 20 and IQ at 8 to 10 years of age. Authors did not present the equation representing the relationship. Using the linear regression function on the extracted data, it was determined that for every 1 pmol/L change in fT4 there is an estimated 2.6 point change in IQ.	*Further analysis was performed* to estimate the incremental impact doses of perchlorate (using the BBDR model) have on IQ

[a] Model adjusted for maternal age; income; employment status at 6 months; country of birth; Diet Quality Index; delivery complications; Peabody Picture and Vocabulary Test (PPVT) score; child 5-minute Apgar score, hospitalization at 1 year; number of children in home at 1 and 2 years, home density at 2 years, family structure at 1 year; and season of assessment.
[b] Model adjusted for age, gender, demographic characteristics (e.g., birth order, ethnicity) and pregnancy characteristic (e.g., BMI and diabetes).

ED_005043_00079783-00106

Study	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at p < 0.05	Study Summary	EPA Evaluation

[c] Fully adjusted model adjusted for maternal psychiatric history, province of birth, and maternal smoking.

[d] Model adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.

[e] Expressive language delay at 30 months was defined as an expressive vocabulary score below the 15th age- and gender-specific percentile or no word combinations

[f] Model adjusted for maternal age, education, pre-natal distress, pre-natal smoking, birthweight, gestational age at blood sampling, and child ethnicity.

[g] Model adjusted for gestational age, maternal age, smoking, BMI, parity, education level, ethnic origin, fetal sex, and birthweight.

[h] Model adjusted for child age, sex, ethnic background, and parity, and maternal education level, smoking history, psychopathologic symptoms in pregnancy, age, marital status, household income, BMI, and gestational age at the time of blood sampling for maternal thyroid function data.

[i] Model adjusted for maternal age; gestational age at birth; birthweight; child age at time of IQ test; maternal fT4, fT4, and TSH various times during gestation; maternal urinary iodide excretion; family socioeconomic status; maternal parity; sex of child; breastfeeding; major maternal stressful life-events; and maternal/parental education.

[j] Model adjusted for maternal education, ethnicity, BMI, and depressive symptomatology.

[k] Model adjusted for gestation length, age at testing, sex, maternal education, and ethnicity.

[l] Based on digitization of figures representing correlation analysis presented in the paper.

[m] Model adjusted for maternal depression, psychosocial factors, tobacco and alcohol use during pregnancy, and demographic variables.

[n] Model was adjusted for child's sex, ethnicity, gestational age at birth, and birthweight, maternal age, educational level, smoking history, pre-natal psychopathology, thyroid medication during pregnancy, parity, marital status, folate and C-reactive levels in early pregnancy, and time of thyroid sampling, and paternal age. According to the study authors "the B's are not interpretable, as the mathematically transformed scores were used in the analyses" (p.6).

[o] The study author presented results using fT4 units of ng/dL. EPA converted to pmol/L using a conversion factor of 12.87 (CTDS Laboratories) for comparison to BBDR output.

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5.4 Findings Related to Categorical Analyses Supporting MCLG Development Based on Avoiding Hypothyroxinemia

Given the SAB's recommendation to concentrate on sensitive populations, one of which are the fetuses of hypothyroxinemic mothers, it is also useful to evaluate the impact of maternal hypothyroxinemia as evaluated by the studies identified in both Group 1 and Group 2 (keeping in mind some Group 1 studies included analysis on both continuous and categorical measures of fT4). That is, in Section 5.3, the evaluation of the papers was specific to the concentration-response functions present in the analyses based on a continuous measure of thyroid hormone levels. However, of specific interest may be how neurodevelopmental outcomes vary when comparing offspring of hypothyroxinemic mothers to those of non-hypothyroxinemic mothers. Table 23 presents a summary of the findings of studies that evaluate the impact of maternal hypothyroxinemia, as a categorical variable, on adverse neurodevelopmental outcomes in offspring, including IQ and performance on the BSID.

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). These findings are supported by two meta-analyses of Fan and Wu (2016) and Wang et al. (2016). These studies found that hypothyroxinemia was associated with a 5.7 point lower score on intelligence tests and a three-fold increased risk of delayed cognitive development in children, respectively. The only studies that did not find a statistically significant effect on any of the evaluated endpoints in Table 23 are Grau et al. (2015) and Craig et al. (2012). As previously discussed Grau et al. (2015) has a high hypothyroxinemic cut point (13.7 pmol/L), and individuals are not iodine deficient. Craig et al. (2012) did find lower fT4 to be associated with lower PDI and MDI; however, this result does not reach statistical significance. Craig et al. (2012) measured fT4 levels during the second trimester (exact gestational weeks not stated).

Additionally, studies identified in the literature review that are not summarized in Table 23 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). These studies demonstrate the sensitivity of the offspring of hypothyroxinemic mothers to adverse neurodevelopmental effects. An approach to inform the derivation of an MCLG based on avoiding hypothyroxinemia is presented in Section 7.

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Table 23. Summary of Studies That Compared Neurodevelopment Outcomes (BSID or IQ) in the Offspring of Hypothyroxinemic (hX) and Non-Hypothyroxinemic Mothers

Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
MDI Score Using Bayley Scale								
Costeira et al. 2011	Portuguese mother-child pairs from iodine-deficient region	fT4 < 10th percentile (< 11.6) (n = 8)	tT4, fT4, tT3, and fT3 between 50th to 90th percentile (n = 36)	t-test on difference between mean scores[a]	24 months	-10.8 (CI: NR) points lower MDI in hX group	> 0.05	< 15
Craig et al. 2012	Mother-child pairs in Maine	fT4 ≤ 3rd percentile (< 11.8) (n = 98)	ft4 between 10th and 90th percentile (1.00 – 1.37 ng/dL or 12.87 – 17.63 pmol/L) (n = 98)	mean matched differences[b]	24 months	-1.4 (-4.9, 2.0) points lower MDI in hX group	0.43	15-29
Júlvez et al. 2013	Spanish mother-child pairs	fT4 < 10th percentile (< 8.89) (n = 164)[c]	fT4 > 10th percentile (n = 1,643)	multivariate linear regression[d]	14 months	-2.2 (-4.47, -0.01) points lower MDI in hX group	NR	Median 13, range 8-20
Li et al. 2010	Chinese mother-child pairs	tT4 < 101.79 nmol/L (n = 19)	matched controls with tT4 > 101.79 nmol/L (n = 38)	t-test on difference between mean scores	25-30 months	-9.3 points lower MDI in hX group	0.004	16-20
Pop et al. 1999	Dutch mother-child pairs	fT4 < 10th percentile (10.4) (n = 22) at 12	fT4 >10th percentile (10.4 pmol/L)	t-test on difference between mean scores[e]	10 months	NR because did not find a statistically significant difference	NR	12

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Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
		GW	(n = 198)					
Pop et al. 2003	Dutch mother-child pairs	fT4 < 10th percentile (12.4 pmol/L) (n = 57)	fT4 > 10th percentile (12.4 pmol/L) (n = 58)	t-test on difference between mean scores	12 months	-10 (-4, -16) points lower MDI in hX group	0.004	12
Psychomotor Development Index (PDI) Using Bayley Scale								
Costeira et al. 2011	Portuguese mother-child pairs from iodine-deficient region	fT4 < 10th percentile (< 11.6) (n = 8)	tT4, fT4, tT3, and fT3 between 50th to 90th percentile (n = 36)	t-test on difference between mean scores[a]	24 months	-13.6 (CI: NR) points lower PDI score in hX group	< 0.05	< 15
Craig et al. 2012	Mother-child pairs in Maine, matched on fT4 levels	fT4 ≤ 3rd percentile (< 11.8) (n = 98)	ft4 between 10th and 90th percentile (1.00 – 1.37 ng/dL or 12.87 – 17.63 pmol/L) (n = 98)	mean matched differences[b]	24 months	-1.9 (-6.1, 2.4) points lower PDI score in hX group	0.39	15-29
Júlvez et al. 2013	Spanish mother-child pairs	fT4 < 10th percentile (< 8.89) (n = 164)[c]	fT4 > 10th percentile (n = 1,643)	multivariate linear regression[d]	14 months	0.28 (-1.94 to 2.51) points higher in PDI score in hX group	NR	Median 13, range 8-20
Li et al. 2010	Chinese mother-child pairs	tT4 < 101.79 nmol/L (n = 19)	matched controls with tT4 > 101.79 nmol/L	t-test	25-30 months	-7.6 (CI: NR) points lower PDI score in hX group	0.007	16-20

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Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
			(n = 38)					
Pop et al. 1999	Dutch mother-child pairs	fT4 < 10th percentile (10.4) (n = 22) at 12 GW	fT4 >10th percentile (10.4 pmol/L) (n = 198)	t-test on difference between mean scores[e]	10 months	-7.4 (-1.1, -13.9) points lower PDI score in hX group	NR	12
Pop et al. 2003	Dutch mother-child pairs	fT4 < 10th percentile (12.4 pmol/L) (n = 57)	fT4 > 10th percentile (12.4 pmol/L) (n = 58)	t-test on difference between mean scores	24 months	-10 (-6, -16) points lower PDI score in hX group	0.005	12
Intelligence Quotient								
Ghassabian et al. 2014	3,727 Dutch mother-child pairs	fT4 < 5th percentile (< 10.99) (n = 129)	fT4 > 5th percentile (> 10.99 pmol/L) (n = 3,598)	multivariate linear regression	6 years	-4.32 (-6.68, -1.81) IQ points lower in hX group	0.001	mean 13.5, range 5.1–17.9
Grau et al. 2015	289 Spanish mother-child pairs	fT4 < 10th percentile (< 13.7) (first trimester) (n = 42)	UIC > 150 g/L, fT4 > 10th percentile and TPO Ab negative (n = 39)	multivariate ANOVA	1 year	2.7 (CI: NR) IQ points higher in the hX mothers[g]	0.419	end of the 1st trimester
Korevaar et al. 2016[h]	3,839 Dutch mother-child	≤ 10th percentile (n = 386)	fT4 between 10th and 90th percentile	multivariate ANOVA	Median 6 years (range 5.6-7.9 years)	-1.8 (0, -3.2) point loss in low fT4 group compared to control	0.05	9-18

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Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
	pairs		(n = 3,288)[i]			group[j]		

NR = not reported; hX = hypothyroxinemia; GW = Gestational Weeks.
[a] Model adjusted for maternal age, parity, socioeconomic-cultural status, length of breastfeeding, use of alcohol and tobacco during pregnancy, children's sex, gestational age, type of delivery, Apgar score, birthweight, body length, and head circumference.
[b] Result adjusted for gestational age, child's age at testing, maternal weight, and years of education.
[c] n for each group is estimated based on the knowledge that analysis is for individuals with fT4 less than 10th percentile and there are 1,642 people in the regression analysis.
[d] Results adjusted for region, sex, psychologist administering IQ test, gestational age and weight at birth, circulating vitamin D during pregnancy and year –season of sampling, urine cotinine levels during pregnancy, TSH, maternal education, parental social class, quality of the test, and child neurologic pathology.
[e] Model adjusted for maternal depression, psychosocial factors, tobacco and alcohol use during pregnancy, and demographic variables.
[f] Model adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.
[g] Results from first trimester, total mean WISC, Table 4 of Grau et al. (2015).
[h] Data are taken from Supplemental Figure 2 of Korevaar et al. (2016).
[i] Reference group is calculated as the total population without the mothers less than or equal to the 10th percentile, and after exclusion of women with *in vitro* fertilization treatment (N = 76) or women with known thyroid disorders or thyroid interfering medication usage (N = 89). Data are taken from Supplemental Figure 2.
[j] Model adjusted for gestational age, maternal age, smoking, BMI, parity, education level, ethnic origin, fetal sex, and birthweight.

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5.5 Summary of Literature Review Findings to Connect Alterations in Thyroid Hormone Levels to Alternations in Neurodevelopment

In this literature review, 15 papers were identified as potentially having data or presenting analysis that may inform the quantitative understanding of the incremental changes in thyroid hormone levels and subsequent adverse neurodevelopmental outcomes. Of these 15 papers, 5 were deemed useful for further quantitative analysis (see Table 22). 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). Further information on Group 1 and Group 2 studies that examined associations of thyroid hormone/hypothyroxinemia is detailed in Appendix G and is organized by neurodevelopmental endpoint.

In subsequent sections, two approaches are presented to link perchlorate doses to alterations in neurodevelopment, via alterations in thyroid hormone levels. Section 6 presents the approach to connect changes in fT4 with changes in neurodevelopment as estimated by the 5 Group 1 studies identified as including data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment in offspring. In Section 7, an alternative option using the BBDR model is presented to evaluate a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate.

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6. Informing the Derivation of an MCLG: Neurodevelopmental Effects

Based on the studies identified for additional quantitative analysis in Section 5, this section presents potential approaches to connect perchlorate exposure and alterations in fT4 levels in pregnant women as predicted by the BBDR model to potential adverse neurodevelopmental impacts in the offspring. 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 changes in neurodevelopment of her child.

The BBDR model is capable of predicting fT4 levels at various gestational weeks of pregnancy for various iodine intake levels. For the purposes of this report, one gestational week was selected from each study of interest for analysis based on when fT4 values were collected. Given that none of the studies identified for additional quantitative analysis are specific to a specific iodine intake level, analyses were conducted to evaluate the impact of perchlorate on the potentially sensitive population of individuals with low iodine intake. That is, the analyses were conducted for individuals with an assumed iodine intake of 75 μg/day as discussed in Section 3.4. Further, to evaluate the impact of fT4 at various percentiles, EPA used the derived fT4 distributions (as described in Section 4) and calculated the resulting changes in the outcome of interest based on effect measures from the study of interest. Central, lower, and upper-bound effect estimates from the 95% CIs were used in all analyses.

An overview of the approach is presented in Figure 12. While Figure 12 is specific for estimating neurodevelopmental effects for the low-iodine intake population, the same process could be followed for any iodine intake level that is output from the BBDR model. Analyses based on the results from each study are presented in alphabetical order.

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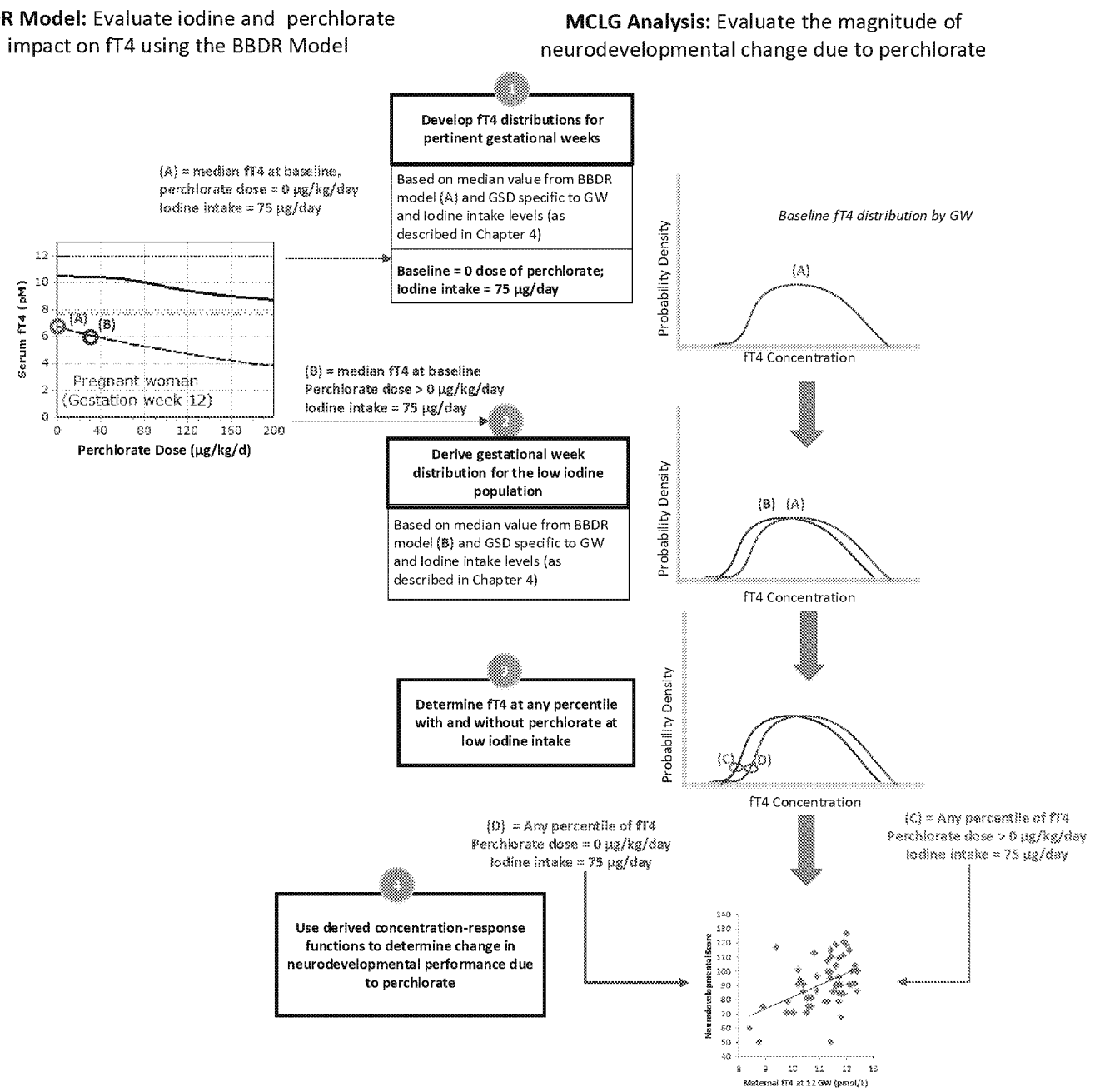
Figure 12. Outline of Approach to Assess the Effect of Doses of Perchlorate on Potential Neurodevelopmental Outcomes



6.1 Analysis Using Finken et al. (2013)

As described in Section 5.3.2, Finken et al. (2013) found an association between decreased fT4 levels and increased standard deviation of reaction time. This association, according to Finken et al. (2013) "…has been found to be related more strongly to individual difference in intelligence, cognitive aging, and neurological disorders" (Finken et al., 2013, p. 1419). This relationship was described in Table 13, from Finken et al.'s (2013) multivariate regression analysis, which found that for every decrease in fT4 there is a subsequent increase in the SD of reaction time with β = -4.9 (-9.5; -0.2), holding all else equal. This function was derived from and is thus applicable to the entire range of fT4 values in Finken et al. (2013). It is unclear exactly what the entire range encompasses but the 2.5th percentile is reported as 6.5 pmol/L and the interquartile range presented in the paper is 8.7 to 10.5 pmol/L.

Using the predicted changes in fT4 for increasing doses of perchlorate output by the BBDR model and estimating different distributional baselines, the following function can be used to estimate changes in the SD of reaction time as associated with changes in fT4:

$$\Delta \text{SD Reaction Time (ms)} = \beta \times \Delta \text{ fT4}$$

Where:

β = -4.9 (95% CI: -9.5, -0.2)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

To evaluate the impact of changes in fT4 levels due to perchlorate on the SD of reaction time using the function estimated in Finken et al. (2013), gestational week 13 fT4 output from the BBDR model was used (see Section 3.4). Estimated fT4 levels at various percentiles were also used (see Section 4.2). Gestational week 13 was selected because the median week of fT4 collection in the Finken et al. (2013) study was 12.9 (IQR: 11.9–14.3).

Results of an analysis demonstrating how increasing perchlorate dosage increases the SD of reaction time are presented in Table 24.

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Table 24. Estimated Change in the Standard Deviation of Reaction Time (milliseconds) based on Finken et al. (2013) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ RTSD Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ RTSD Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ RTSD Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.93	N/A	8.78	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	6.74	N/A	7.41	N/A	8.84	N/A
1	6.69	0.26 (0.01, 0.51)	7.35	0.29 (0.01, 0.56)	8.77	0.34 (0.01, 0.66)
2	6.64	0.51 (0.02, 0.99)	7.29	0.56 (0.02, 1.09)	8.71	0.67 (0.03, 1.30)
3	6.59	0.75 (0.03, 1.45)	7.24	0.82 (0.03, 1.59)	8.64	0.98 (0.04, 1.90)
4	6.54	0.97 (0.04, 1.89)	7.19	1.07 (0.04, 2.07)	8.58	1.28 (0.05, 2.48)
5	6.50	1.19 (0.05, 2.31)	7.14	1.31 (0.05, 2.54)	8.52	1.56 (0.06, 3.03)
10	6.30	2.15 (0.09, 4.18)	6.92	2.37 (0.10, 4.59)	8.27	2.83 (0.12, 5.48)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.2 Analysis Using Korevaar et al. (2016) and an EPA analysis of Korevaar et al. (2016)

As summarized in Section 5.3.2, Korevaar et al. (2016) presented a spline model and a multivariate regression with a quadratic term (Table 17) to explain the relationship between maternal fT4 and child IQ, which they found both to have an inverted U-shaped association. Korevaar provided EPA with complete study data[24], and subsequently EPA confirmed the authors' conclusion that the regression analysis with the quadratic term sufficiently explained the relationship between maternal fT4 and child IQ assessed with the spline model.

6.2.1 Analysis with Quadratic Function from Korevaar et al. (2016)

Given the adequate fit of the quadratic regression model, EPA used the quadratic equation coefficients put forth in Table 17 to determine the changes in child IQ for given changes in maternal fT4. The following function was used to determine the change in child IQ for a given change in maternal fT4 due to perchlorate:

$$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$$

[24] Data were provided by Dr. Tim Korevaar on February 6, 2017

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Where:

β_1 = 33.81 (95% CI: 9.8, 57.82)

β_2 = -6.235 (95% CI: -10.567, -1.903)

$fT4_1$ = fT4 when perchlorate dose = 0 µg/kg/day at a given fT4 percentile for the low iodine intake population.

$fT4_2$ = fT4 when perchlorate dose is at a defined dose, X, which is greater than 0 µg/kg/day, for the low iodine intake population.

To evaluate the impact of perchlorate induced changes in fT4 levels on IQ using the estimated function from Korevaar et al. (2016), gestational week 13 fT4 output from the BBDR model was used (see Section 3.4), along with the estimated fT4 levels at various percentiles (see Section 4.2). Gestational week 13 was selected because the median week of fT4 collection in this study was 13.2 weeks (range 9-18 GW). The results of this analysis are presented in Table 25.

Table 25. Estimated Change in IQ, based on Independent Analysis of Korevaar et al. (2016) Central, Lower and Upper Quadratic-Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.93	N/A	8.78	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	6.74	N/A	7.41	N/A	8.84	N/A
1	6.69	-0.08 (0.24, -0.40)	7.35	-0.07 (0.26, -0.40)	8.77	-0.05 (0.29, -0.39)
2	6.64	-0.16 (0.47, -0.79)	7.29	-0.14 (0.50, -0.78)	8.71	-0.10 (0.56, -0.77)
3	6.59	-0.23 (0.69, -1.16)	7.24	-0.21 (0.74, -1.15)	8.64	-0.15 (0.82, -1.13)
4	6.54	-0.31 (0.90, -1.51)	7.19	-0.27 (0.96, -1.50)	8.58	-0.20 (1.08, -1.48)
5	6.50	-0.38 (1.11, -1.86)	7.14	-0.33 (1.18, -1.85)	8.52	-0.25 (1.32, -1.82)
10	6.30	-0.70 (2.01, -3.42)	6.92	-0.62 (2.14, -3.39)	8.27	-0.48 (2.40, -3.35)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.2.2 EPA Independent Analysis of Korevaar et al. (2016) Data

Given the interest in the effect of maternal fT4 on child IQ at the lower end of the fT4 distribution for the purposes of informing the derivation of an MCLG for perchlorate, EPA conducted an additional analysis of the Korevaar et al. (2016) data. The additional analysis focuses only on the maternal fT4

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values in the lower range of the distribution (i.e., the left-hand side of the inverted U shape). With the complete Korevaar et al. (2016) dataset provided by the study author it was possible to specifically evaluate the relationship between maternal fT4 and child IQ on the lowest end of the fT4 distribution using the same sample from the study that excluded those with pre-existing thyroid disease (i.e., Figure 7 C).

Since the curve estimated in the Korevaar et al. (2016) spline analysis has an inflection point at the 50th percentile of fT4, both a bivariate and a multivariate linear regression of natural log maternal fT4 on child IQ were evaluated that only analyzed participants whose fT4 levels were below the median level to capture the lower range of the distribution. This median value was reported in the paper as 14.9 pmol/L. Analysis of the data demonstrated the median to more precisely be estimated as 14.883 pmol/L[25]. The regression analyses were conducted using the same multiply imputed dataset the authors used in their original analysis, using the same covariates as were used in the original study (gestational age at blood sampling, maternal age, smoking status, BMI, parity, education level, ethnic origin, fetal sex, and birthweight). Linear ordinary least squares regressions were chosen for estimation, as the Korevaar et al. (2016) analysis suggests the relationship between fT4 and IQ would only be parabolic over the entire range of fT4 values, and the relationship between fT4 and IQ reported in the paper remains positive at all points below the 50th percentile of fT4.

The underlying function for the multivariable model to predict IQ is:

$$IQ = \beta_0 + \beta_1 * \ln(fT4) + \beta_2 * x_2 \ldots + \beta_{10} * x_{10} + \varepsilon$$

Where:

β_0 = intercept

β_1- β_{10} = coefficients;

fT4 = fT4 level for a given dose of perchlorate (pmol/L)

$x_2 - x_{10}$ represent gestational age at blood sampling (weeks), maternal age (years), smoking status (no/previous/current), BMI, parity, education level, ethnic origin, fetal sex, and birthweight (kg), respectively, and ε represents the error where ε are assumed to be normally distributed with mean zero and constant variance.

The underlying function for the bivariate model is:

$$IQ = \beta_0 + \beta_1 * \ln(fT4) + \varepsilon$$

Where:

β_2 = intercept

β_1 = Coefficient associated with ln(fT4)

[25] The 14.883 pmol/L fT4 level is between the 98th and 99th percentile of the median iodine distribution predicted by the BBDR model and is greater than any value predicted by the BBDR model in the 75 µg/day population distributions, estimated as explained in Section 4.

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fT4 = fT4 level for a given dose of perchlorate (pmol/L)

To utilize β_1 to gain an understanding of the impact of changes in perchlorate doses on fT4, as predicted by the BBDR model, on changes in IQ the following function was used:

$$\Delta IQ = \beta_1 * \ln\left(\frac{fT4_{increasedClO4}}{fT4_{baselineClO4}}\right)$$

Estimated coefficients and 95% confidence intervals are presented in Table 26 from both the bivariate and multivariate linear regressions of maternal fT4 on child IQ, focusing on the lower 50th percentile of data.

Table 26. Coefficient Estimates from Linear Regression Analyses of Lower 50th Percentile of fT4 of Korevaar et al. (2016) Data

Analysis	Child IQ: β_1 (95% CI)	*p*-value
Bivariate Maternal ln fT4 on Child IQ	8.38 (2.54, 14.22)	0.005
Multivariate Maternal ln fT4 on Child IQ	4.63 (-0.52, 9.78)	0.078

N = 1,916 mother-child pairs.
Maternal fT4 levels were transformed by the natural logarithm.
Multivariate analysis adjusted for gestational age, maternal age, smoking status, BMI, parity, education, ethnicity, gender of the infant, and birthweight.
This is a novel analysis of the lower 50th percentile of fT4 of Korevaar et al. (2016).

As expected, results of the regression analyses show a relationship between maternal fT4 and child IQ. Both the bivariate and multivariate models suggest that child IQ is higher on average as maternal fT4 is higher during early pregnancy. The multivariate model is borderline statistically significant.

Results of an analysis demonstrating how increasing perchlorate dosage decreases IQ based on EPA's analysis of the Korevaar et al. (2016) data are presented in Table 27 using the multivariate beta estimates and in Table 28 using the bivariate beta estimates. Multivariate beta estimates are further evaluated as they account for potential confounders in the relationship between fT4 and IQ. The bivariate beta estimates are also included as this result demonstrated statistical significance, however it does not account for potential confounding variables.

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Table 27. Estimated Change in IQ, based on Independent Analysis of Korevaar et al. (2016) Central, Lower, and Upper Multivariate-Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.93	N/A	8.78	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	6.74	N/A	7.41	N/A	8.84	N/A
1	6.69	-0.04 (0.00, -0.08)	7.35	-0.04 (0.00, -0.08)	8.77	-0.04 (0.00, -0.08)
2	6.64	-0.07 (0.01, -0.15)	7.29	-0.07 (0.01, -0.15)	8.71	-0.07 (0.01, -0.15)
3	6.59	-0.11 (0.01, -0.22)	7.24	-0.11 (0.01, -0.22)	8.64	-0.11 (0.01, -0.22)
4	6.54	-0.14 (0.02, -0.29)	7.19	-0.14 (0.02, -0.29)	8.58	-0.14 (0.02, -0.29)
5	6.50	-0.17 (0.02, -0.36)	7.14	-0.17 (0.02, -0.36)	8.52	-0.17 (0.02, -0.36)
10	6.30	-0.31 (0.04, -0.66)	6.92	-0.31 (0.04, -0.66)	8.27	-0.31 (0.04, -0.66)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

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Table 28. Estimated Change in IQ, based on Independent Analysis of Korevaar et al. (2016) Central, Lower and Upper Bivariate-Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.93	N/A	8.78	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	6.74	N/A	7.41	N/A	8.84	N/A
1	6.69	-0.07 (-0.02, -0.11)	7.35	-0.07 (-0.02, -0.11)	8.77	-0.07 (-0.02, -0.11)
2	6.64	-0.13 (-0.04, -0.22)	7.29	-0.13 (-0.04, -0.22)	8.71	-0.13 (-0.04, -0.22)
3	6.59	-0.19 (-0.06, -0.33)	7.24	-0.19 (-0.06, -0.33)	8.64	-0.19 (-0.06, -0.33)
4	6.54	-0.25 (-0.08, -0.43)	7.19	-0.25 (-0.08, -0.43)	8.58	-0.25 (-0.08, -0.43)
5	6.50	-0.31 (-0.09, -0.52)	7.14	-0.31 (-0.09, -0.52)	8.52	-0.31 (-0.09, -0.52)
10	6.30	-0.57 (-0.17, -0.96)	6.92	-0.57 (-0.17, -0.96)	8.27	-0.57 (-0.17, -0.96)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.3 Analysis using Pop et al. (1999, 2003)

As summarized in Section 5.3.2, two Pop et al. papers found a relationship between fT4 and neurodevelopmental outcomes measured using the BSID. Specifically, Pop et al. (1999, 2003) found a relationship between changes in fT4 and PDI. Pop et al. (2003) also found a relationship between fT4 and MDI. Using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Microsoft® Excel, effect estimates were estimated based on a bivariate linear regression analysis. The effect estimates and their associated 95% CIs are summarized in Table 29.

Table 29. Pop et al. (1999, 2003) Effect Estimates[a]

Study/Endpoint	β (95% CI)
Pop et al. (1999)/PDI	8.5 (95% CI: 0.01, 17.0)
Pop et al. (2003)/PDI	8.4 (95% CI: 4.0, 12.8)
Pop et al. (2003)/MDI	6.3 (95% CI: 1.9, 10.6)

[a] All estimates are based on bivariate regression analysis of digitized data.

These Pop et al. (1999, 2003) functions are specific to the individuals in their sample who were hypothyroxinemic. In Pop et al. (1999) the 10th percentile hypothyroxinemic cut point corresponded with an fT4 level of 10.4 pmol/L, and in Pop et al. (2003) this corresponded with an fT4 level of 12.4 pmol/L. The 10.4 pmol/L level is between the 43rd and 44th percentile of the median iodine intake and

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between the 87th and the 88th percentile of the 75 µg/day iodine intake distributions predicted by the BBDR model and estimated distribution as explained in Section 4. The lowest fT4 level evaluated in Pop et al. (1999) was 7.86 pmol/L[26]. The 12.4 pmol/L level is equivalent to between the 84th and 85th percentile of the median iodine intake and between the 99th and 99.5th percentile of the 75 µg/day iodine intake distributions estimated predicted by the BBDR model and estimated distribution as explained in Section 4. The lowest fT4 level evaluated in Pop et al. (2003) was 8.39 pmol/L[26].

To evaluate the impact of the changes in fT4 levels due to perchlorate on MDI and PDI using the Pop et al. (1999, 2003) studies, EPA used gestational week 12 fT4 output from the BBDR model (see Section 3.4), along with the estimated fT4 levels at various percentiles (see Section 4.2). This is because gestational week 12 is when Pop et al. (1999, 2003) measured fT4 levels in their study populations. The subsequent subsections outline the specific analysis and results for each study/endpoint combination from the Pop et al. (1999, 2003) analyses.

6.3.1 Analysis for Pop et al. (1999) - PDI

To evaluate the impact that a change in fT4 as a result of an increased dose of perchlorate will have on resulting PDI scores based on Pop et al. (1999), the following equation was utilized:

$$\Delta PDI = \beta \times \Delta fT4 \ (fT4 \text{ in pmol/L})$$

Where:

β = 8.5 (95% CI: 0.01, 17.0)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

Results of an analysis demonstrating how increasing perchlorate dosage decreases PDI based on Pop et al. (1999) are presented in Table 30.

[26] This value was extracted from the digitized data sets from the Pop et al. (1999, 2003) analyses.

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Table 30. Estimated Change in PDI, Based on Pop et al. (1999) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.95	N/A	8.80	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	6.75	N/A	7.41	N/A	8.85	N/A
1	6.70	-0.46 (0.00, -0.92)	7.35	-0.50 (0.00, -1.01)	8.78	-0.60 (0.00, -1.21)
2	6.65	-0.90 (0.00, -1.79)	7.30	-0.98 (0.00, -1.97)	8.71	-1.17 (0.00, -2.35)
3	6.60	-1.31 (0.00, -2.62)	7.24	-1.44 (0.00, -2.88)	8.65	-1.72 (0.00, -3.44)
4	6.55	-1.71 (0.00, -3.42)	7.19	-1.88 (0.00, -3.75)	8.59	-2.24 (0.00, -4.48)
5	6.51	-2.09 (0.00, -4.18)	7.14	-2.29 (0.00, -4.59)	8.53	-2.74 (0.00, -5.47)
10	6.31	-3.77 (0.00, -7.53)	6.93	-4.14 (0.00, -8.27)	8.27	-4.94 (-0.01, -9.88)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.3.2 Analysis for Pop et al. (2003) – PDI

To evaluate the impact that a change in fT4 as a result of an increased dose of perchlorate will have on resulting PDI scores based on Pop et al. (2003), the following equation was utilized:

$$\Delta PDI = \beta \times \Delta fT4 \ (fT4 \text{ in pmol/L})$$

Where:

β = 8.4 (95% CI: 4.0, 12.8)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

Results of an analysis demonstrating how increasing perchlorate dosage decreases PDI based on Pop et al. (2003) are presented in Table 31.

Table 31. Estimated Change in PDI, Based on Pop et al. (2003) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.95	N/A	8.80	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	6.75	N/A	7.41	N/A	8.85	N/A
1	6.70	-0.45 (-0.22, -0.69)	7.35	-0.50 (-0.24, -0.76)	8.78	-0.60 (-0.28, -0.91)
2	6.65	-0.89 (-0.42, -1.35)	7.30	-0.97 (-0.46, -1.48)	8.71	-1.16 (-0.55, -1.77)
3	6.60	-1.30 (-0.62, -1.98)	7.24	-1.42 (-0.68, -2.17)	8.65	-1.70 (-0.81, -2.59)
4	6.55	-1.69 (-0.80, -2.57)	7.19	-1.85 (-0.88, -2.83)	8.59	-2.21 (-1.05, -3.37)
5	6.51	-2.06 (-0.98, -3.14)	7.14	-2.27 (-1.08, -3.45)	8.53	-2.70 (-1.29, -4.12)
10	6.31	-3.72 (-1.77, -5.67)	6.93	-4.09 (-1.95, -6.23)	8.27	-4.88 (-2.32, -7.44)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.3.3 Analysis for Pop et al. (2003) – MDI

To evaluate the impact that a change in fT4 as a result of an increased dose of perchlorate will have on resulting MDI scores based on Pop et al. (2003), the following equation was utilized:

$$\Delta MDI = \beta \times \Delta fT4 \text{ (} fT4 \text{ in pmol/L)}$$

Where:

β = 6.3 (95% CI: 1.92, 10.6)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

Results of an analysis demonstrating how increasing perchlorate dosage decreases MDI based on Pop et al. (2003) are presented in Table 32.

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Table 32. Estimated Change in MDI, based on Pop et al. (2003) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ MDI Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ MDI Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ MDI Central (Lower, Upper)[1]
Iodine Intake = 170 µg/day						
0	7.95	N/A	8.80	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	6.75	N/A	7.41	N/A	8.85	N/A
1	6.70	-0.34 (-0.10, -0.57)	7.35	-0.37 (-0.11, -0.63)	8.78	-0.45 (-0.14, -0.75)
2	6.65	-0.66 (-0.20, -1.12)	7.30	-0.73 (-0.22, -1.23)	8.71	-0.87 (-0.27, -1.46)
3	6.60	-0.97 (-0.30, -1.64)	7.24	-1.07 (-0.33, -1.80)	8.65	-1.27 (-0.39, -2.14)
4	6.55	-1.27 (-0.39, -2.13)	7.19	-1.39 (-0.42, -2.34)	8.59	-1.66 (-0.51, -2.79)
5	6.51	-1.55 (-0.47, -2.60)	7.14	-1.70 (-0.52, -2.86)	8.53	-2.03 (-0.62, -3.41)
10	6.31	-2.79 (-0.85, -4.70)	6.93	-3.07 (-0.93, -5.16)	8.27	-3.66 (-1.12, -6.16)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.4 Analysis Using Vermiglio et al. (2004)

As summarized in Section 5.3.2, Vermiglio et al. (2004) found a direct relationship between fT4 levels and IQ. Using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Microsoft® Excel, effect estimates were estimated based on a bivariate linear regression analysis. Specifically, for every decrease in fT4 there was an associated decrease in IQ with β = 2.6 (95% CI: 0.90-4.34).

To evaluate the impact that a resulting change in fT4 from an increased dose of perchlorate will have on resulting IQ scores, the following function was utilized:

$$\Delta IQ = \beta \times \Delta fT4$$

Where:

β = 2.6 (95% CI: 0.90, 4.3)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

This function was derived for the entire range of fT4 in Vermiglio et al. (2004) which is estimated to be 8.22 pmol/L to 17.8 pmol/L. To evaluate the impact of changes in fT4 levels due to perchlorate on IQ using Vermiglio et al. (2004) gestational week 16 fT4 output from the BBDR model was used.

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Gestational week 16 was chosen because the Vermiglio et al. (2004) function is based on gestational week 20 data, but the BBDR model is only able to estimate fT4 results out to gestational week 16.

Results of an analysis demonstrating how increasing perchlorate dosage decreases IQ based on Vermiglio et al. (2004) are presented in Table 33.

Table 33. Estimated Change in IQ, based on Vermiglio et al. (2004) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[1]
Median I Intake = 170 µg/day						
0	7.88	N/A	8.63	N/A	10.25	N/A
Low I Intake = 75 µg/day						
0	6.72	N/A	7.30	N/A	8.56	N/A
1	6.67	-0.13 (-0.05, -0.22)	7.25	-0.14 (-0.05, -0.24)	8.49	-0.17 (-0.06, -0.28)
2	6.62	-0.25 (-0.09, -0.42)	7.20	-0.28 (-0.10, -0.46)	8.43	-0.32 (-0.11, -0.54)
3	6.57	-0.37 (-0.13, -0.62)	7.15	-0.41 (-0.14, -0.68)	8.37	-0.48 (-0.16, -0.79)
4	6.53	-0.49 (-0.17, -0.81)	7.10	-0.53 (-0.18, -0.88)	8.32	-0.62 (-0.21, -1.03)
5	6.49	-0.60 (-0.21, -0.99)	7.05	-0.65 (-0.22, -1.08)	8.27	-0.76 (-0.26, -1.27)
10	6.30	-1.09 (-0.38, -1.81)	6.85	-1.18 (-0.41, -1.97)	8.03	-1.38 (-0.48, -2.31)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.5 Uncertainties Related to the Approach

The approach presented in this report is 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. Uncertainties associated with the BBDR model and derivation of the distribution of fT4 have been discussed previously (see Sections 3.5 and 4.3, respectively). 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. For example, since the literature review for this report has ceased at least two additional articles have been published evaluating the relationship between maternal fT4 and adverse behavioral outcomes (Endendijk, Wijnen, Pop, & van Baar, 2017; Oostenbroek et al., 2017). The impact of future research on this assessment is unknown.

This section will focus on the uncertainties related to the literature identified that connects the estimated maternal fT4 levels with offspring neurodevelopmental outcomes and the subsequent quantitative analysis. Specifically, the first sections (Section 6.5.1 through 6.5.5) discuss uncertainties

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as they pertain to the attributes set forward in Section 5.2.3. Sub-section 6.5.6 discusses uncertainties related to the underlying quantitative analyses.

6.5.1 Population For Which Dose-Response Information is Available

The majority of Group 1 studies presented analyses using the full range of maternal fT4 for the population to assess incremental changes as they relate to subsequent neurodevelopment of their offspring, this is compared to evaluating incremental changes in maternal fT4 only in the hypothyroxinemic range. This may help to explain why many of the studies identified in the literature review did not find a statistically significant relationship between continuous maternal fT4 and neurodevelopment. As demonstrated in Korevaar et al. (2016), there may be an ideal range of maternal fT4 values and the greatest impact of change will occur when maternal fT4 values fall below or above that range. When comparing offspring of mothers that experienced hypothyroxinemia to those that did not, adverse neurodevelopmental outcomes were more consistently related to exposure to maternal hypothyroxinemia, compared to looking evaluating incremental changes in maternal fT4 across the full spectrum. Thus, uncertainty exists as to whether the studies evaluating the full spectrum of fT4 are underestimating the impact of fT4 on neurodevelopment for the sensitive population of the fetuses of hypothyroxinemic pregnant women.

Further, none of the current studies analyzed in Section 6 are based on a U.S. population. The data from all papers with the exception of Vermilgio 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. In a recent analysis of NHANES data, Caldwell et al. (2013) found that the median urinary iodide excretion level in women aged 20-39 was 113 µg/g creatinine. Murray et al. (2008) estimated the lower- and upper-bound mean iodine intakes for U.S. women aged 25-45 as approximately 145 to 197 µg/day, which is in line with the studies of Dutch women by Brussaard et al. (1997) and Verkaik-Kloosterman et al. (2010). Thus, there is little reason to believe that the uncertainty in iodine intake levels would have a large impact on the resulting derivation of an MCLG.

In Vermiglio et al. (2004), urinary iodide at the time of pregnancy for the iodine sufficient area was 95.2 (SD: 55.8) µg/day and 48.1 (SD: 38.2) µg/day in the iodine-deficient area. Comparing this information to the Caldwell et al. (2013) data, urinary iodide levels from Vermiglio et al. (2004) were lower than urinary iodide levels in the United States, even in the iodine-sufficient areas.[27] It is unclear

[27] The urinary iodide excretion levels in the Vermiglio et al. (2004) study were reported in units of µg/d, while the Caldwell et al. (2013) results were reported in units of µg/g creatinine. These units can be

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how the lower urinary iodide levels may reflect a difference in the populations and the extent this difference would have on extrapolating the Vermiglio et al. (2004) results to the U.S. population. Korevaar et al. (2016) provided urinary iodide data for only 672 women in their studies. The mean reported urinary/creatinine ratio in this subsample was 227 μg/g, which is much higher than that presented in Caldwell et al. (2013) for U.S. women.

The influence of nationality on endpoints and examinations used to evaluate them may produce uncertainty when comparing study populations. For example, in Pop et al. (1999, 2003) and other Dutch studies, the Dutch version of the BSID was used to evaluate neurodevelopmental endpoints. The Dutch version of the BSID is a translation of the U.S. version and uses the same cut points for impairment (Pop et al., 2003; van der Meulen & Smrkovsky, 1984). However, Dutch norms may differ from U.S. norms and one study found that "for all subtests… these differences are clinically relevant" (Steenis, Verhoeven, Hessen, & van Baar, 2015).

6.5.2 The Endpoint Evaluated

The majority of neurodevelopmental indicators tests used in the five studies measure indices of global neuropsychological performance. However, animal data show that thyroid hormone decrement affects different brain areas depending on the stage of gestation when hormone deficiency is present (Morreale de Escobar et al., 2004). As such, global markers may not be evaluating the most sensitive neurodevelopmental endpoint in regard to decreased maternal thyroid hormone levels depending on the phase of gestation in which a fetus may be exposed to low maternal thyroid hormone levels. Further, mothers with pre-existing thyroid disease were excluded from certain studies used in the analysis (e.g., Korevaar et al., 2016; Finken et al., 2013) which may have potentially reduced the relationship between fT4 and neurodevelopmental outcomes in these studies. Additionally, 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.

6.5.3 Iodine Intake Data for the Study Population

None of five studies carried forward for additional quantitative analysis had information specifically on iodine intake levels, though Vermiglio and Korevaar et al. (2016) both had some data on urinary iodine as discussed in Section 6.5.1. Therefore, uncertainty exists regarding how information culled from each study relates to a specific iodine intake rate, and the corresponding fT4 changes, as predicted by the BBDR model.

6.5.4 Size of the Study Population

The analyses of Pop et al. (1999; 2003) and Vermiglio et al. (2004) have small ($n < 30$) populations when considering the results used for quantitative analysis. However, despite a small sample size and low statistical power, the studies found statistically significant relationships between fT4 and a measure of neurodevelopment. Additionally, the Pop et al. (1999, 2003) findings of an association between maternal hypothyroxinemic levels of fT4 and adverse neurodevelopmental outcomes are

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converted using an estimate of daily creatinine excretion, which is assumed to be 1 gram in adult women (van Rees-Wortelboer et al., 1987). Thus, in this population, urinary iodide excretion levels expressed as μg/day and μg/g are assumed equal.

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supported by many other papers (i.e., the majority of Group 1 and Group 2 papers). Finken et al. (2013) and Korevaar et al. (2016) both used larger cohorts (n > 1,700 for both) in the analyses EPA used to evaluated incremental changes in neurodevelopment.

6.5.5 The Method and Timing of Maternal fT4 Measurement During Pregnancy

All studies identified for further quantitative analysis on the relationship between maternal fT4 and neurological effects in the offspring evaluated this relationship based on a one-time fT4 level measurement during pregnancy. From evaluating the 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). While maternal hypothyroxinemia later in pregnancy appears to be less influential, it is not without effect. For example, Pop et al. (2003) found a dependent relationship between neurological deficits in children associated with decreases in the mother's first-trimester fT4 (at 12 gestational weeks). However, when they followed women to week 32 they found that those women whose fT4 reverted to the normal range did not have children with MDI/PDI deficits. This rebound of fT4 occurred in at least 15 of the 57 cases that were part of the cohort that informed the function derived from Pop et al. (2003). Additionally, the authors found that individuals born to mothers with consistently low fT4 had the worst neurodevelopmental outcomes. This represents an uncontrolled source of variability given that what happens after week 12 to maternal fT4 levels appears to have an impact on neurodevelopmental outcome, but the data that are available to inform a dose-response are only for week 12 fT4 measurements.

This uncontrolled variability is present in all the studies used for analysis given that they all compare fT4 levels at only one point in pregnancy to neurodevelopmental outcomes. If low fT4 later in pregnancy also causes further damage beyond the effects in the first trimester, it is likely that a steeper dose-response slope would have been found if only those women who were consistently hypothyroxinemic throughout pregnancy were evaluated (see Pop et al., 2003, Figure 3). This weakening of the correlation between hormone and outcome is likely to lessen the perchlorate dose-response slope on neurodevelopment because it relies on both the relationship between perchlorate's effect on hormones (BBDR model) and then hormones' effect on outcome.

Also related to the method of assessing fT4 is that uncertainties exist in regard to the analytical approach to evaluating fT4 levels. Although a working group was put together by the International Federation of Clinical Chemistry and Laboratory Medicine in 2005 to standardize thyroid function tests primarily for TSH and fT4, this standardization has not yet been achieved (Thienpont, Faix, & Beastall, 2015). As such, assay results obtained at different times or in different countries may not be directly comparable due to differences in analytical procedures. fT4 could be as little as 1% of the circulating total T4 concentration (Koulouri, Moran, Halsall, Chatterjee, & Gurnell, 2013), making it difficult to measure. The bulk of the enzyme-linked immunosorbent assays used for measurement of fT4 require no pre-treatment or serum extraction procedures to be undertaken. Rather, they rely on competitive binding assays that could be affected by changes in endogenous serum protein ratios, displacing agents such as heparin, and the presence of other antibodies that may block the action of the assay antibody (Koulouri et al., 2013). Correlation between liquid chromatographic tandem mass spectrometry (MS) values versus standard immunoassay techniques showed that there was a correlation coefficient of approximately 0.75 for fT4, unlike total T4, which had a correlation coefficient of 0.91-0.95. This was likely due to the ability of tandem MS to better measure fT4 compared to immunoassay (Jonklaas et al., 2014). In regards to the studies further evaluated for

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quantitative assessment, both Pop et al. studies used immunoassay techniques to assess the fT4 levels in their cohort, Korevaar et al. (2016) and Finken et al. (2013) used chemiluminescence assays, and Vermiglio et al. (2004) used commercial kits supplied by Kodak Clinical Diagnostic Ltd., Amersham, U.K. Additionally, there could be individual variation in fT4 measurements or interference from some over-the-counter medications, such as aspirin and other NSAIDs, which could displace thyroid hormones on TBG or TTR, causing artificial elevations in fT4 measurement (Koulouri et al., 2013). Thus, the true fT4 levels of the subjects in the papers used for further analysis may differ from the values obtained in their analyses. However, 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.

6.5.6 Uncertainties Related to the Quantitative Analyses

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. The reason for this result is the log distribution assumed when developing the distribution around fT4, and the approach to developing distributions for each dose of perchlorate. Specifically, as the mean value of fT4 is decreased due to perchlorate, the distribution of fT4 is decreased by a consistent ratio. Subsequently, for the functions based on the change in fT4, changes at lower percentiles require smaller unit changes to result in the consistent ratio where changes at higher percentiles require greater unit changes to result in the consistent ratio. This also explains why the results for EPA's independent analysis of Korevaar et al. (2016), which are dependent on the percent change in fT4 as opposed to the unit change in fT4, are consistent across percentiles.

An additional uncertainty consideration, specifically when evaluating the lower percentiles of fT4 from the derived distributions, is the potential for extrapolating beyond the data from which the function was derived. For example, Table 34 summarizes the lowest fT4 value observed in each of the studies further evaluated by EPA. Given that a lower fT4 level is associated with worse neurodevelopmental outcomes, there is no reason to believe that predictions of fT4 effect on neurodevelopment are being overestimated by falling below the observed range.

Table 34. Lowest Observed fT4 levels in Group 1 Studies Used for Analysis

Study	Lowest Observed fT4 (pmol/L)
Finken et al. (2013)[1]	< 6.5
Korevaar et al. (2016)	6.38
Pop et al. (1999)[2]	7.86
Pop et al. (2003)[2]	8.39
Vermiglio et al. (2004)[2]	8.22

[1] Full range not presented. 6.5 pmol/L represents the 2.5th percentile fT4.
[2] Range of data estimated from digitized data set.

Further, several of the dose-response functions presented in this report linking maternal fT4 to an offspring's neurodevelopment are based on EPA's own digitization of data from a figure depicting a

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correlation or regression analysis (Pop et al., 1999, 2003; Vermiglio et al., 2004). The EPA analysis has not used multi-regression analysis to adjust for confounding or interacting variables because it does not have the raw data to do so. However, as discussed in Section 5.3, Pop et al. (2003) took steps to mitigate the potential for residual confounding during the development of the cohorts for which they conducted their evaluation. Specifically, women were excluded from analysis due to pregnancy and child outcome-related factors that could interfere with a child's neurodevelopmental outcome. For example, women were excluded if they had at least one episode of reported post-partum depression. Additionally, as outlined in the Pop et al. (1999) summary, in their logistic regression analysis they found a much higher relative risk after controlling for confounding variables (RR = 5.8; 95% CI: 1.3-12.6) compared to their univariate analysis (RR = 3.6; 95% CI: 1.1-12.1). This implies that the current effect estimates derived from the Pop et al. studies may be underestimating the true effect of fT4 level in the maternal hypothyroxinemic range and their impact on neurodevelopment. Vermiglio et al. (2004) did not provide any discussion or analysis relating to the lack of control for confounding variables. The analyses provided by Korevaar et al. (2016) and Finken et al. (2013) did control for confounding variables, and beta estimates were either provided in the primary studies or calculated by EPA with the underlying dataset.

Additionally, some studies that were not used for further quantitative analysis found associations which were attenuated when adjusting models for potential confounders (e.g., Gyllenberg et al., 2016; Modesto et al., 2015) given the impact variables such as smoking may have on both thyroid hormone levels and neurodevelopmental outcomes. For example, in Gyllenberg et al. (2016) an association between fT4 and risk of schizophrenia was observed in their unadjusted analysis, but after individually adjusting for maternal smoking during early gestation and collectively adjusting for maternal psychiatric history, province of birth, and maternal smoking, the association between maternal hypothyroxinemia and offspring schizophrenia was no longer significant (Table 14). The adjustment for maternal smoking resulted in a greater than 20% change in the odds ratio. According to the authors, the finding that the continuous measure of fT4 lost statistical significance while there was still an association between maternal hypothyroxinemia after adjusting for confounders "suggests that the relationship between maternal fT4 and schizophrenia is present only when fT4 levels are below a particular threshold" (Gyllenberg et al., 2016, p. 966). Other factors that were not measured or controlled by the papers assessed, such as maternal lead or arsenic levels, are additional sources of uncontrolled variability that would tend to weaken the correlation between fT4 and neurodevelopment and thus perchlorate and neurodevelopment.

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7. Informing the Derivation of an MCLG: Hypothyroxinemia

The previous section outlined a process by which the output of the BBDR model was connected to neurodevelopmental outcomes in the offspring of pregnant women who are exposed to perchlorate in pregnancy. This connection was made by using epidemiologic literature to connect shifts in fT4, as predicted by the BBDR model, to various indicators of neurodevelopment.

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. 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, as outlined in Section 5.4.

For example, in evaluating the Group 2 studies, 13 of the 14 studies evaluated maternal hypothyroxinemia (or fT4 level) and neurocognitive outcomes. Eleven of these 13 studies found an increased risk of adverse neurodevelopmental outcomes in the offspring of mothers with maternal hypothyroxinemia, compared to non-hypothyroxinemic mothers. These effects included decreased performance on the Bayley Scales for Infant Development (Craig et al., 2012; Costeira et al., 2011; Júlvez et al., 2013; Li et al., 2010), the McCarthy Scales of Children's Abilities (Suárez-Rodríguez, Julián, and Aguilar, 2012) and behavioral assessment scales (Kooistra et al., 2006). This is in addition to the increased risk of expressive language delay and nonverbal cognitive delay (Ghassabian, Henrichs, and Tiemeier, 2014) and increased fetal and infant head size (van Mil et al., 2012). Additionally, Päkkilä et al. (2015) found increased odds of having repeated a school class as assessed in 16-year-olds. Further, two meta-analyses (Fan and Wu, 2016; Wang et al., 2016) concluded that low fT4 is associated with adverse neurodevelopmental outcomes including increased risk of delayed cognitive development, and lower intelligence and motor scores.

In addition to presenting regression analyses that evaluated how thyroid hormone levels impact neurodevelopment, 10 Group 1 studies also found strong associations between maternal hypothyroxinemia and neurodevelopment outcomes in offspring when compared to non-hypothyroxinemic groups. That is, of the 11 studies in Group 1 that performed a categorical analysis, the only study that did not find an adverse association between maternal hypothyroxinemia and a measure of neurodevelopment was Oken et al. (2009). As previously discussed, this study only evaluated T4, not fT4 which may be an explanation for the null finding.

In evaluating neurodevelopment with the Bayley Scales, both Pop et al. studies (1999, 2003) found the relationship between reduced fT4 and reduced MDI or PDI only in hypothyroxinemic first-trimester pregnant mothers. Further, both Ghassabian et al. (2014) and Korevaar et al. (2016) found maternal hypothyroxinemia to be associated with lower non-verbal intelligence scores in offspring compared to IQ scores from offspring of non-hypothyroxinemic mothers. Finken et al. (2013) found increased baseline reaction time and standard deviation of reaction time in offspring of hypothyroxinemic mothers compared to non-hypothyroxinemic mothers. Henrichs et al. (2010) found exposure to maternal hypothyroxinemia *in utero* to be associated with an increased odds of expressive language and nonverbal cognitive delays when compared to non-exposed offspring. Additionally, Gyllenberg et al. (2016) found a statistically significant association between exposure to maternal hypothyroxinemia and odds of being diagnosed with schizophrenia, while Román et al. (2013) found

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that maternal hypothyroxinemia was associated with increased odds of having a probable autistic child. Further, Modesto et al. (2015) found a relationship between ADHD and severe maternal hypothyroxinemia.

This section presents and alternative population-based approach that estimates the shift in the population of hypothyroxinemic, pregnant women for a specific gestational week that would result from perchlorate exposure. Specifically, an approach is outlined by which the baseline fT4 distribution for the median iodine intake from the BBDR model is evaluated to determine the hypothyroxinemic cut point based on this distribution. In this report, EPA assumed that hypothyroxinemia occurs at the 10th percentile fT4 level. Then, by evaluating predicted fT4 distributions for the 75 μg/day of iodide (low iodine intake) population with various perchlorate doses, the increase in the proportion of the population below the hypothyroxinemic cut point is determined. This approach is presented visually in Figure 13.

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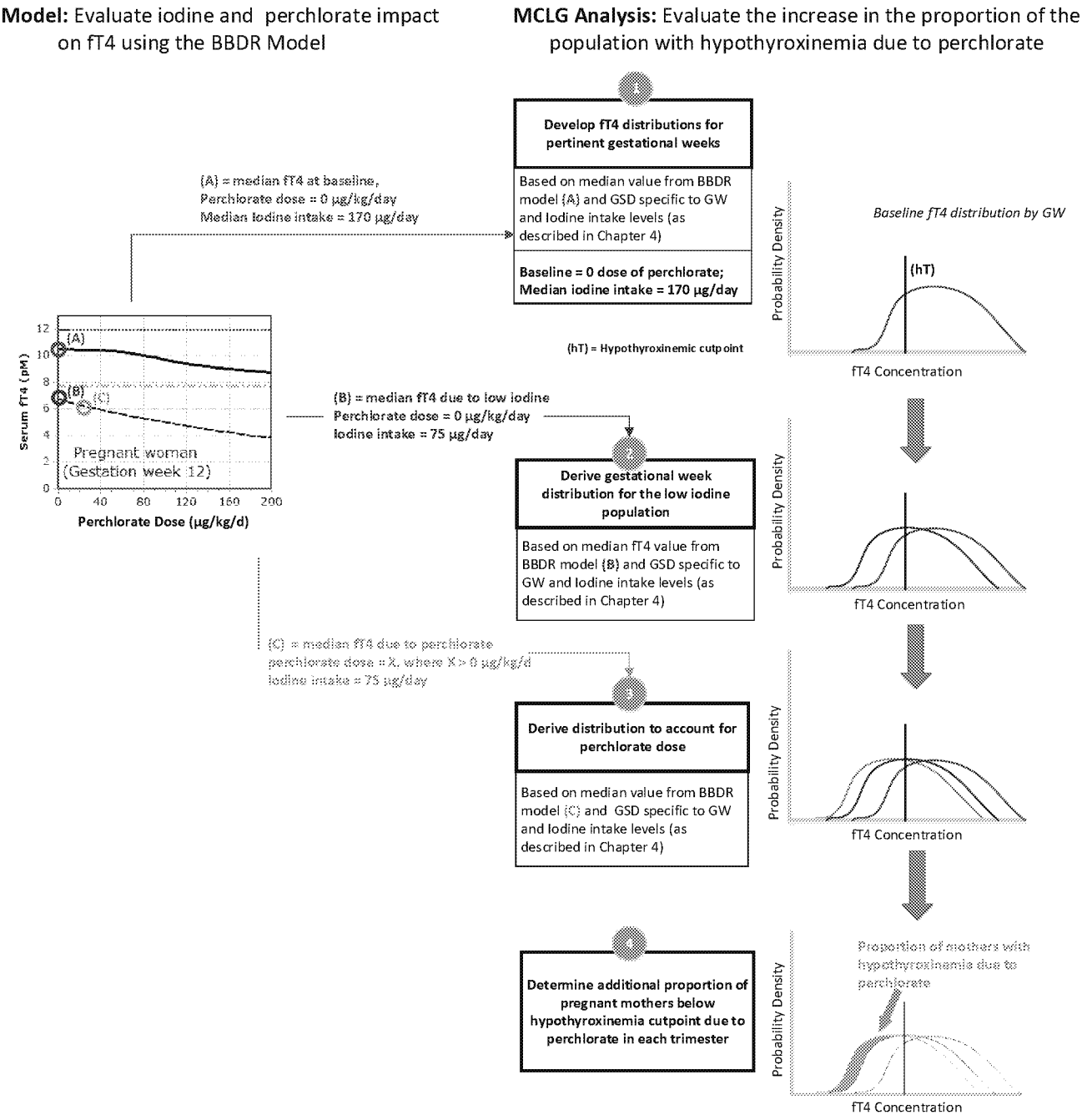
Figure 13. Outline of Approach to Determine the Proportion of Pregnant Mothers That Are Below a Hypothyroxinemic Cut Point Due to Perchlorate



7.1 Evaluation of the Shift Early Pregnancy Mothers into the Hypothyroxinemic Range

Given that the majority of studies presented in Table 23 measured fT4 levels in early pregnancy around the 12, 13, or 16 weeks, these are the weeks concentrated on for this analysis as well.

To evaluate how the proportion of women with hypothyroxinemia changes based on perchlorate, it is necessary to evaluate the fT4 distributions derived in Section 4. Specifically, once the fT4 distribution for each gestational week, for the median iodine intake population is estimated (as presented in Table 6, Table 7, and Table 8), it is possible to determine the definition of hypothyroxinemia for each gestational week. That is, defining hypothyroxinemia as the 10th percentile of the median-iodine intake population, a cut point for hypothyroxinemia can be set for each gestational week[28]. These cut points are presented in column 1 of Table 35.

Based on this hypothyroxinemic cut point, the proportion of people in the low-iodine intake population that would be considered hypothyroxinemic before any exposure to perchlorate was then assessed. This was done by evaluating the entire distribution of fT4 for the low-iodine population to identify the percentile that aligns with the median-iodine hypothyroxinemic cut point fT4 concentration presented in column 1 of Table 35. This percentile represents the proportion of individuals in the low-iodine group who are considered hypothyroxinemic before any perchlorate exposure. This proportion is presented in column 2 of Table 35. It is now possible to isolate the impact of perchlorate on the low-iodine population with respect to the resulting increase in the proportion of individuals with hypothyroxinemia. Based on the proportion of individuals identified in column 2 of Table 35 it is now possible to evaluate the full distributions of fT4 for given doses of perchlorate to determine when there is a 1% or 5% increase in the proportion of individuals with hypothyroxinemia. The results of this analysis are presented in columns 3 and 4, respectively, of Table 35.

Table 35. Summary of Results for the Amount of Perchlorate Needed to Increase the Proportion of Low Iodine Intake, Hypothyroxinemic Individuals by a Defined Percentage

Gestational Week	fT4 (pmol/L) at the Hypothyroxinemic Cut Point (i.e.,10th Percentile of 170 µg/day Iodine Intake Group) (Column 1)	Corresponding Percentile in 75 µg/day Iodine Intake Group (Column 2)	Perchlorate Dose (µg/kg/day) Associated with a 1 Percent Increase in Proportion Hypothyroxinemic (Column 3)	Perchlorate Dose (µg/kg/day) Associated with a 5 Percent Increase in Proportion Hypothyroxinemic (Column 4)
12	8.80	48.4	0.4	2.2
13	8.78	47.9	0.4	2.2
16	8.63	52.6	0.3	2.1

[28] The 10th percentile cut off was selected as an example. The impact of varying this cut point based on other percentiles is presented in Section 7.2.

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7.2 Uncertainties in the Results Pertaining to Evaluating the Proportion of Individuals Below a Hypothyroxinemic Cut Point

In determining the proportion of a population that would be considered hypothyroxinemic there are several uncertainties. For example, there is uncertainty with respect to determining the appropriate effect size to constitute an "adverse" effect or at least an effect that may have some biological consequence. For a continuous parameter with a defined baseline distribution, a cut point at the tail of the distribution (e.g., 5th or 10th percentile) is often used to distinguish between within and outside the reference or "normal" range. The idea is that it is desirable to have individuals within the reference range because those at the extreme of the distribution may already have or be more susceptible to developing clinical disease. The 10th percentile cut point was used to define hypothyroxinemia and is not based upon a specific clinical endpoint (e.g., goiter). The exact cut point does not affect this analysis significantly if the measure of effect is the shift in the tail end of fT4 and its relationship with neurodevelopment or the shift in the tail (cut point) of the distribution. This can be seen in Table 36 and Table 37 which demonstrate an analogous analysis, but using the 2.5th or 5th percentile as the defined cut point for hypothyroxinemia, respectively. These tables demonstrate the dose of perchlorate associated with a 1 percent increase in the proportion of individuals who would be considered hypothyroxinemic ranges from 0.3 μg/kg/day to 0.5 μg/kg/day, depending on the cut off used and gestational week of interest. Additionally, the results range from 2.1 to 2.8 μg/kg/day when evaluating the dose of perchlorate associated with a 5 percent increase in the proportion of individual that are hypothyroxinemic, depending on the cut off used and gestational week of interest.

The reason for the minimal effect is that there will be members of the population just above the 5th or 10th percentile whom perchlorate would have the opportunity to affect and place into the range of concern regardless of where the cut point is set. However, if the determinant is whether perchlorate would move the median individual out to the cut point, a much greater effect size (and thus dose) is needed and the decision of 5th, 10th, or some other cut point would have a large bearing on the perchlorate dose needed to produce the hypothyroxinemic state. This is important in this analysis, as different populations vary widely in their distribution of fT4 levels.

Further, intra-individual variance in fT4 may also be a factor affecting the tail of the distribution, as about 10% of the population variance is made up of intra-individual variance (Andersen et al., 2002). Thus, 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.

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Table 36. Summary of Results for the Amount of Perchlorate Needed to Increase the Proportion of Low Iodine Intake, Hypothyroxinemic Individuals by a Defined Percentage: Hypothyroxinemic Cut Point at 2.5th Percentile fT4 of 170 µg/day Iodine Intake Group

Gestational Week	fT4 (pmol/L) at the Hypothyroxinemic Cut Point (i.e., 2.5th Percentile of 170 µg/day Iodine Intake Group)	Corresponding Percentile in 75 *µg/day* Iodine Intake Group	Perchlorate Dose (µg/kg/day) Associated with a 1 Percent Increase in Proportion Hypothyroxinemic	Perchlorate Dose (µg/kg/day) Associated with a 5 Percent Increase in Proportion Hypothyroxinemic
12	7.95	21.8	0.5	2.8
13	7.93	21.5	0.5	2.8
16	7.88	25.1	0.4	2.4

Table 37. Summary of Results for the Amount of Perchlorate Needed to Increase the Proportion of Low Iodine Intake, Hypothyroxinemic Individuals by a Defined Percentage: Hypothyroxinemic Cut Point at 5th Percentile fT4 of 170 µg/day Iodine Intake Group

Gestational Week	fT4 (pmol/L) at the Hypothyroxinemic Cut Point (i.e., 5th Percentile of 170 µg/day Iodine Intake Group)	Corresponding Percentile in 75 µg/day Iodine Intake Group	Perchlorate Dose (µg/kg/day) Associated with a 1 Percent Increase in Proportion Hypothyroxinemic	Perchlorate Dose (µg/kg/day) Associated with a 5 Percent Increase in Proportion Hypothyroxinemic
12	8.33	32.9	0.4	2.3
13	8.32	32.9	0.4	2.3
16	8.22	37.1	0.3	2.1

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8. Other Health Effects Potentially Associated with Perchlorate

The competitive inhibition of the NIS by perchlorate largely results in health effects associated with hypothyroxinemia or hypothyroidism. Perchlorate has the potential to affect other organ systems that contain NISs, such as the salivary glands, gastric mucosa, ovaries, lactating breast tissue, and placenta (Portulano, Paroder-Belenitsky, & Carrasco, 2014), though few studies have linked perchlorate to effects on these organ systems. Perchlorate may also cause oxidative stress (Schreinemachers, Ghio, Sobus, & Williams, 2015; Zhao, Zhou, Chen, Li, & Ding, 2015). The body contains a number of antioxidant defenses that act to attenuate this damage, but chronic low-dose exposure to environmental toxicants could have a range of adverse outcomes (Tyrrell, Melzer, Henley, Galloway, & Osborne, 2013), some of which cannot be immediately predicted from the recognized mode of action. Currently, there is limited evidence to implicate chronic low-dose exposure to perchlorate in causing disease states other than hypothyroxinemia and hypothyroidism; however, evidence does suggest the need for further studies to determine processes other than competitive inhibition of the NIS that may occur (ATSDR, 2008).

This section provides a brief overview of the potential adverse health effects that could be related to perchlorate, given what is known regarding its mode of action. These health effects are not captured in the analysis of approaches for potentially informing the derivation of a perchlorate MCLG. This information provides context for the limited data on the full potential adverse health effects of perchlorate. The information presented here supports the idea that protecting against the shift into a hypothyroxinemic state, or the subsequent adverse neurologic impacts resulting from that shift in fT4, may also protect against other adverse health effects of which EPA is not yet fully aware.

8.1 Hypothyroidism

Endocrine systems are to some extent capable of adapting to environmental stressors. The negative feedback loop that drives the HPT axis is highly nuanced, and the easiest components to measure are circulating levels of T4, T3, and TSH. The system is also capable of self-regulating other components that are harder to measure, including receptor numbers, upregulating deiodinases, and changing plasma concentrations of carrier proteins such as TBG, TTR, and albumin (Zoeller et al., 2007). This type of compensatory mechanism has been observed in human perchlorate dosing studies (Braverman et al., 2006; Greer et al., 2002; Lawrence et al., 2000). There were no measurable changes in TSH, T3, or T4 despite reduced uptake of iodide in the two-week studies (Greer et al., 2002; Lawrence et al., 2000). It must be noted that, because the adult euthyroid human thyroid contains several months of T4 stored in the colloid, it is not expected that a two-week study would result in a change in thyroid status. On the contrary, in a study with chronic low-dose perchlorate exposure for 6 months, the authors suggested continued compensation for reduced iodide uptake because there were no changes in radiolabeled iodide uptake or thyroid hormone measurements (Braverman et al., 2006). However, the sample size for the Braverman et al. study was low (n = 13; double-blind, randomized trial). Also, urinary iodide among participants in this study was considerably higher than the national average (mean 257.8 µg/total volume before 0.5 mg dose of perchlorate; mean 311.5 µg/total volume before 3 mg dose of perchlorate).

If there is a TSH-independent upregulation of NIS expression, it is unclear how long this can continue based on the available literature. However, it is apparent that at some point, the HPT axis is unable to adapt, and negative correlations between thyroid function and perchlorate begin to emerge (Blount et al., 2006; Steinmaus et al., 2007; Steinmaus et al., 2016). As stated by EPA in the chemical

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assessment of perchlorate, "sustained changes in thyroid hormone and TSH secretion can result in thyroid hypertrophy and hyperplasia, possibly followed by hypothyroidism in people unable to compensate with an increase in thyroid iodide uptake" (U.S. EPA, 2005, p. 14). That is, given perchlorate's known mode of action, it is biologically plausible that perchlorate could be associated with hypothyroidism, especially in individuals without the ability to adequately respond to perchlorate's effect.

8.2 Cardiovascular Disease

Relatively small increases in TSH within the reference range have implications for cardiovascular health (Taylor, Razvi, Pearce, & Dayan, 2013). Biomarkers such as total serum cholesterol, low-density lipoprotein (LDL) cholesterol level, and triglycerides have been shown to increase in response to increases in TSH (Asvold, Vatten, Nilsen, & Bjoro, 2007; Canaris, Manowitz, Mayor, & Ridgway, 2000). Additionally, changes in thyroid hormones can damage the heart and vasculature (Suh & Kim, 2015). Even subclinical hypothyroidism could impair ventricular relaxation and filling, decrease exercise tolerance, affect cardiomyocyte function, and affect vascular smooth muscle (Danzi & Klein, 2014; Suh & Kim, 2015). Competitive binding of perchlorate to the thyroid NIS can cause increases in circulating TSH. If chronic perchlorate exposure occurs, TSH may become elevated for sufficient durations to alter circulating lipids and affect cardiac function.

8.3 Other Potential Diseases

The primary mode of action of perchlorate is its competitive inhibition of thyroid uptake of iodide; however, like many other persistent environmental toxicants such as PCBs, perchlorate also acts as an oxidizing agent (U.S. EPA, 2016). Oxidants, such as oxides, peroxides, and superoxides, are constantly being generated through normal metabolic processes; as a result, there are a suite of mechanisms to mitigate and eliminate these potentially harmful ions. Chronic perchlorate exposure, even at low levels, may cause oxidative damage to organ systems and may result in an array of adverse health effects. Additionally, while the thyroid NIS is the most active in the body, NISs are also found in ovaries, breast tissue during lactation, placenta, salivary gland, and gastro-intestinal tract (Portulano et al., 2014). Low levels of iodide uptake in NISs outside the thyroid gland suggest that there could be additional potential adverse outcomes beyond those outlined in this document due to alterations in thyroid hormone homeostasis.

Further, the potential for adverse effects resulting from gene–environment interactions is plausible. The Comparative Toxicogenomics Database (CTD) (MDI Biological Laborarotory, 2016) describes some potential risks posed by chemicals, including perchlorate, based on the genes and mutations reported to be impacted across a range of species. Searching this database for information on perchlorate provides results that are useful to help understand the range of the potential health effects related to perchlorate exposure. For example, the CTD has identified 455 diseases potentially associated with perchlorate. According to the CTD, mechanistic correlations have been reported for perchlorate exposure and thyroid diseases such as goiter and hypothyroidism, as well as necrosis, hypertrophy, and jaw abnormalities. However, there is a much larger number of diseases for which a link has been postulated based on knowledge that perchlorate can alter a specific gene's expression[29]

[29] The CTD provides data on the genes found to interact with a compound of interest, then identifies the manuscripts that show disease states resulting from changes in regulation of those genes. It provides details

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and that those alterations in expression (not specifically related to perchlorate) have been associated with a variety of adverse health outcomes. Adverse health outcomes based on these alterations range from neurodegenerative disease to cancer. However, as stated by EPA's Integrated Risk Information System program, "perchlorate is not likely to pose a risk of thyroid cancer in humans, at least at doses below those necessary to alter thyroid hormone homeostasis, based on the hormonally-mediated mode of action in rodent studies and species differences in thyroid function" (U.S. EPA, 2005, p. 12).

Additionally, 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 adverse health effects associated with perchlorate.

on other compounds that cause similar gene changes and metabolic pathway interactions, and lists exposure studies and results.

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9. Conclusion

This draft report describes a proposed methodology that follows the SAB recommendation to inform development of an MCLG for perchlorate (SAB, 2013). The methodology assesses perchlorate exposure by examining predicted impacts on maternal fT4 levels in pregnant women prior to mid gestation and subsequent adverse neurodevelopmental impacts in their offspring. Additionally, an approach is presented that does not directly quantify neurodevelopmental impacts but evaluates a shift in fT4 into a hypothyroxinemic state, which may increase the risk of neurodevelopmental impacts. All of the approaches evaluate effects at low iodine intakes, considering a distribution of fT4 level. This is opposed to the more common approach of exploring the effect of a contaminant on a mean individual from a sensitive life stage. In taking this distributional approach, EPA is able to isolate and explore the impact of perchlorate on a more sensitive group of individuals. This decreases but does not eliminate the uncertainty associated with ensuring that an MCLG protects the most sensitive population with a margin of safety.

To develop the proposed methodology for informing the derivation of an MCLG, EPA conducted a literature review to identify studies that could connect the output of the BBDR model to neurodevelopmental effects. In reviewing this literature, EPA identified five studies from which a further analysis could be done to evaluate incremental changes in fT4 and associated neurodevelopmental changes. Additionally, 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 (See Section 5.4).

Using the BBDR model, and the five studies identified the Agency prepared an analysis that characterize how much neurodevelopmental outcomes are expected to change given decreased iodine intake and increased perchlorate exposure. The Pop et al. (1999, 2003) relationships for PDI may be the most sensitive in regard to the change predicted in the neurodevelopmental outcome. This may be due to the fact that this analysis is specifically on the hypothyroxinemic population. Korevaar et al. (2016) shows the least change in regard to the change in IQ for the doses of perchlorate evaluated.

Results from the analyses of Section 6 are summarized in Table 38. Additional results for other doses of perchlorate, impact using the upper and lower 95 percent confidence intervals, and additional fT4 percentiles are presented in Section 6.

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Table 38. Summary of Estimated Changes in Neurodevelopmental Outcomes based on Central Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at the 50th Percentile of fT4

Dose of Perchlorate (µg/kg/day)	Gestational Week 12				Gestational Week 13					Gestational Week 16	
							Korevaar et al. (2016) ΔIQ[a]				
	fT4 (pmol/L)	Pop et al. (1999) ΔPDI[a]	Pop et al. (2003) ΔPDI[a]	Pop et al. (2003) ΔMDI[a]	fT4 (pmol/L)	Finken et al. (2013) ΔRTSD[a]	Quadratic	EPA Independent Analysis: Bivariate	EPA Independent Analysis: Multivariate	fT4 (pmol/L)	Vermiglio et al. (2004) ΔIQ[a]
Iodine Intake = 170 µg/day											
0	10.67	N/A	N/A	N/A	10.64	N/A	N/A	N/A	N/A	10.25	N/A
Iodine Intake = 75 µg/day											
0	8.85	N/A	N/A	N/A	8.84	N/A	N/A	N/A	N/A	8.56	N/A
1	8.78	-0.60	-0.60	-0.45	8.77	0.34	-0.05	-0.07	-0.04	8.49	-0.17
10	8.27	-4.94	-4.88	-3.66	8.27	2.83	-0.48	-0.57	-0.31	8.03	-1.38

[a] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

Results in Table 39 present the dose of perchlorate associated with a unit change in the endpoint specific to the study of interest. These results provide a different perspective on how to evaluate the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (as predicted by the epidemiologic literature). The same approach was used to estimate these doses as described in Section 6.

Table 39. Predicted Dose of Perchlorate per Unit Change in Neurodevelopmental Measure for Low Iodine Intake Individuals based on Central Effect Estimates at the Median fT4 level

Study	Endpoint	ΔfT4 in pmol/L (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)	Dose of perchlorate per unit change in endpoint (µg/kg/day)[a]
Korevaar et al. (2016) Quadratic	IQ	-1.08 (12.2%)	23
Korevaar et al. (2016) EPA Independent Analysis: Bivariate	IQ	-0.98 (11.1%)	20
Korevaar et al. (2016) EPA Independent Analysis: Multivariate	IQ	-1.66 (18.7%)	45
Vermiglio et al. (2004)	IQ	-0.37 (4.3%)	6.5
Pop et al. (2003)	MDI	-0.15 (1.7%)	2.2
Pop et al. (2003)	PDI	-0.12 (1.3%)	1.7
Pop et al. (1999)	PDI	-0.12 (1.3%)	1.7
Finken et al. (2013)	SD of Reaction Time	-0.21 (2.4%)	3.0
N/A	1% or 5% increase in proportion of hypothyroxinemic pregnant women[b]	N/A	0.3 – 0.4[c] [1%] 2.1 – 2.2[c] [5%]

[a] Based on the regression analysis for the range of fT4 data within each study. Central beta estimates of the low iodide intake population (= 75 µg/day) are presented.
[b] Hypothyroxinemia defined as fT4 < 10th percentile
[c] Range based on gestational week used to perform the analysis (12 to 16 weeks).

Results from the analysis informing the derivation of an MCLG based on the shift in the proportion of individuals having fT4 below a hypothyroxinemic cut point is presented in Table 40 (recreated from Table 35).

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Table 40. Summary of Results for the Amount of Perchlorate Needed to Increase the Proportion of Hypothyroxinemic, Low Iodine Individuals by a Defined Percentage (with hypothyroxinemia defined as fT4< 10th Percentile)

Gestational Week	fT4 (pmol/L) at the Hypothyroxinemic Cut Point (i.e., 10th Percentile of 170 µg/day Iodine Intake Group) (Column 1)	Corresponding Percentile in 75 µg/day Iodine Intake Group (Column 2)[a]	Perchlorate Dose (µg/kg/day) Associated with a 1 Percent Increase in Proportion Hypothyroxinemic (Column 3)[a]	Perchlorate Dose (µg/kg/day) Associated with a 5 Percent Increase in Proportion Hypothyroxinemic (Column 4)[a]
12	8.80	48.4	0.4	2.2
13	8.78	47.9	0.4	2.2
16	8.63	52.6	0.3	2.1

[a] Results based on central effect estimates, pTSH in BBDR model set to 0.398

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Peer Review Draft: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

Volume III
Appendices B–G

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Appendix B – Comparing Predicted fT4 and TSH Changes from Steinmaus et al. (2016) to the BBDR Model Output

To evaluate the BBDR model, EPA compared the predicted changes in both fT4 and TSH from the BBDR model to those seen in the epidemiological literature. Several studies have found impacts of perchlorate on thyroid hormone levels. Specifically, Blount et al. (2006) found women with low urinary iodide to be particularly susceptible to altered thyroid hormone levels with perchlorate exposures. Additionally, Steinmaus et al. (2013) also found an inverse relationship between thyroid hormone levels and perchlorate, and determined populations with concomitant exposures to other goitrogens (i.e., smokers) and low urinary iodide had an increased risk of altered thyroid hormone levels with perchlorate exposure. However, the most appropriate study on which to do this comparison is Steinmaus et al.'s *Thyroid Hormones and Moderate Exposure to Perchlorate during Pregnancy in Women in Southern California* (2016). This study evaluated a large pregnant population with early pregnancy exposure to perchlorate and subsequent thyroid hormone impacts. Therefore, EPA evaluated Steinmaus et al.'s (2016) analysis and results with the aim of comparing the predicted effect estimates relating perchlorate exposure to both fT4 and TSH levels to the effect predicted by the BBDR model.

Overview of Steinmaus et al. (2016)

Steinmaus et al. (2016) evaluated the potential for perchlorate exposure (as measured by urinary perchlorate) to impact thyroid hormone levels (T4, fT4 and TSH) in pregnant women in San Diego. Data were collected as part of Project Baby's Breath during 2000-2003. During this time period the Colorado River, a large source of drinking water in the United States, was contaminated with perchlorate from a perchlorate manufacturing plant. Perchlorate concentrations during this time period in the river were 4 to 8 μg/L. Urine samples were collected from pregnant women at 7 weeks gestation, and blood samples were collected from the same women around 15 to 20 gestational weeks. The median urinary perchlorate concentration in this population was 6.50 μg/L. According to Steinmaus et al. (2016), this is more than double the reported concentration of perchlorate in NHANES from 2001 to 2002. Additional summary statistics on the distributions of key data are presented in Table B-1.

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Table B-1. Distribution of Perchlorate, fT4, TSH and Urinary Iodine in Steinmaus et al. (2016)

Variable	n	Mean ± SD	min	Percentile			max
				25th	50th	75th	
Urinary perchlorate (µg/L)	1,880	8.49 ± 9.86	0.23	3.95	6.50	9.96	177.00
Serum fT4 (ng/dL) (pmol/L)[1]	1,880	0.86 ± 0.19 (11.07 ± 2.45)	0.11 (1.42)	0.77 (9.91)	0.85 (10.94)	0.93 (11.97)	5.44 (70.01)
Serum TSH (µIU/mL)[2]	1,879	1.36 ± 0.86	0.003	0.80	1.20	1.69	8.39
Urinary iodide (µg/L)	1,818	214.9 ± 247.3	0.8	77.0	154.5	270.0	3,000

[1]Calculated by multiplying ng/dL values by 12.87
[2] µIU/mL is equivalent to mIU/L (the units used in the BBDR model)
Source: Table 1 from Steinmaus et al. (2016)

Using multivariate regression analysis, Steinmaus et al. (2016) evaluated the relationship between urinary perchlorate and thyroid hormone levels, specifically fT4, T4, and TSH. In their analysis perchlorate, thiocyanate, creatinine, and TSH were $\log_{10}$-transformed to create normal distributions. Variables included in the final models due to *a priori* decision making included urinary creatinine concentrations, maternal age and education, ethnicity, and gestational age at serum collection. Additionally, the final models were adjusted for urinary thiocyanate, as it changed regression coefficients by more than 10%. Perchlorate-thyroid hormone analyses were also estimated after stratifying by urinary iodide categories of < 100, 100-300, and > 300 µg/day.

The key results from the Steinmaus et al. analysis are presented in Table B-2.

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Table B-2. Regression Coefficients between Maternal log_{10} Urinary Perchlorate Concentrations and Serum Free Thyroxine Concentrations (ng/dL), Thyroxine (µg/dL), and Thyroid Stimulating Hormone (µIU/mL)[a]

Group	n	fT4 (β(95% CI))	T4 (β(95% CI))	log_{10} TSH (β(95% CI))
All subjects	1,476	-0.053 (-0.092, -0.013)	-0.70 (-1.06, -0.34)	0.071 (0.008, 0.133)
Iodine (µg/L)				
< 100	452	-0.022 (-0.100, 0.056)	-0.57 (-1.20, 0.07)	0.034 (-0.081, 0.148)
100-300	698	-0.031 (-0.067, 0.005)	-0.44 (-0.95,0.08)	0.094 (0.002, 0.189)
> 300	326	-0.172 (-0.305, -0.039)	-1.77 (-2.73,-0.81)	0.089 (-0.058, 0.236)

[a] Only includes participants with urinary creatinine concentrations between the 10th and 90th percentiles (i.e., 41-233 mg/dL). All models are adjusted for urinary creatinine, maternal age, maternal education, ethnicity (Hispanic vs. non-Hispanic), gestational age at serum collection and urinary thiocyanate.
Source: Table 3 from Steinmaus et al. (2016)

When evaluating all iodine groups, Steinmaus et al. (2016) found a statistically significant, inverse relationship between perchlorate and thyroid hormone (both fT4 and total T4). Further, there was a statistically significant, directly proportional relationship between perchlorate and log_{10}TSH. Evaluating these results as a whole, it can be seen that perchlorate exposures in the San Diego cohort are associated with depressed fT4, which may in turn be resulting in an increase in TSH. However, this increase in TSH is not compensating for the decreased fT4 as a result of perchlorate exposure. This finding is supported by Fitzgerald and Bean (2016), who evaluated thyroid hormone status in healthy and diseased populations and noted that although changes in T4 (as a result of levothyroxine dosing) have a predictable impact on TSH levels, increasing TSH levels do not have a consistently predictable impact on T4 levels (Fitzgerald & Bean, 2016).

Steinmaus et al. (2016) found the effect of perchlorate on fT4 levels to be similar among women with low (<100 µg/day) and normal (100-300 µg/day) iodine intakes. They found a greater effect of perchlorate on fT4 in the high iodine intake group (>300 µg/day). Their hypothesis for this finding is as follows:

> "In most individuals, very high iodine intakes transiently and paradoxically inhibit thyroid hormone production, termed the acute Wolff–Chaikoff effect (Wolff & Chaikoff, 1948). Normally, this is only temporary, and after a short disruption there is an "escape" and thyroid function returns to normal after a few days, even if high iodine exposure continues (Eng et al., 1999). However, several studies have reported increased rates of thyroid autoimmunity and hypothyroidism in areas where people have chronically high iodine intakes, from diet (e.g., seaweed consumption) or drinking water with naturally high iodine concentrations. This would suggest that chronic excessive high iodine intakes can lead to long-term hypothyroidism in susceptible individuals (Eng et al., 1999; Konno, Makita, Yuri, Iizuka, & Kawasaki, 1994; Li et al., 1987; Y. Li et al., 2010; Pedersen et al., 2007; Tajiri, Higashi, Morita, Umeda, & Sato, 1986; Teng et al., 2006). Associations between very high urinary iodide concentrations and decreased thyroid hormone production have also been seen in NHANES (Cushing, Steinmaus, Miller, & Smith, 2011; Vanderver, Engel, & Lamm, 2007). Overall, these studies, combined with our

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findings, suggest that excessive iodine intakes could lead to altered thyroid function and an enhanced susceptibility to perchlorate. " (p. 865)

Steinmaus et al. (2016) also noted a correlation between perchlorate and iodine. It is difficult to hypothesize why exposure to perchlorate would be correlated with increased iodine levels. However, given this correlation, if individuals with higher perchlorate exposure also had higher iodine intake, there may have been uncontrolled confounding that could have diminished the beta estimate.

Additional analyses were presented evaluating the impact on perchlorate by category of urinary thiocyanate concentration, urinary nitrate concentration, ethnicity, sample collection weeks (weeks between urine and serum sample collection), and TPO-Ab positivity (see Table 3 from Steinmaus et al. (2016) for additional results).

Predicting Changes in fT4 and TSH Using Steinmaus et al. (2016)

Given Steinmaus et al. (2016) did not find a different relationship between perchlorate and fT4 or TSH between low and normal iodine intakes, EPA calculated changes in fT4 and TSH using the all subjects iodine intake models in Table B-2 (first row).

fT4

The underlying function for the Steinmaus fT4 model represents the dependence of fT4 on perchlorate exposure as a slope (β) of the change in fT4 per log10 change in perchlorate urinary concentration:

$$fT4 = \beta \times \left(\log_{10}\left(C_{perchlorate}\right)\right) + y_0 + \alpha$$

Where:

β = -0.053 (-0.092, -0.013) (fT4 measured in ng/dL)

$C_{perchlorate}$= the concentration of perchlorate in urine (µg/L)

y_0 = intercept

α = all other variables in the model

Therefore, to understand the change in fT4 (ΔfT4) due to a change in the concentration of perchlorate in urine from a defined baseline concentration to an increased concentration, the equation becomes:

$$\Delta fT4 = \beta \times \log_{10}\left(\frac{C_{perchlorate,increased}}{C_{perchlorate,baseline}}\right)$$

Where:

β = -0.053 (-0.092, -0.013) (fT4 measured in ng/dL)

$C_{perchlorate,baseline}$ = the concentration of perchlorate in urine (µg/L) at an assumed baseline

$C_{perchlorate,increased}$= the concentration of perchlorate in urine (µg/L) after an increase in exposure

TSH

The underlying function for the Steinmaus TSH model represents the dependence of TSH on perchlorate exposure as a slope (β) of the change in $\log_{10}$TSH per $\log_{10}$ change in perchlorate urinary concentration:

$$log_{10}TSH = \beta \times \left(\log_{10}\left(C_{perchlorate}\right)\right) + y_0 + \alpha$$

Where:

β = -0.071 (0.008, 0.133), (TSH measured in µIU/mL)

y_0 = intercept

$C_{perchlorate}$= the concentration of perchlorate in urine (µg/L)

α = all other variables in the model

Given that TSH was also log transformed predicting ΔTSH can be described through the following steps. First,

$$\frac{TSH_{increased}}{TSH_{baseline}} = \left(\frac{C_{perchlorate,increased}}{C_{perchlorate,baseline}}\right)^{\beta}$$

Where:

$TSH_{baseline}$= the concentration of serum TSH at an assumed baseline

$TSH_{increased}$ = the concentration of serum TSH with an increased exposure to perchlorate

$C_{perchlorate,baseline}$ = the concentration of perchlorate in urine (µg/L) at an assumed baseline

$C_{perchlorate,increased}$= the concentration of perchlorate in urine (µg/L) after an increase in exposure

β = -0.071 (0.008, 0.133) (TSH measured in µIU/mL)

Then $TSH_{increased}$ can be described as:

$$TSH_{increased} = TSH_{baseline} \times \left(\frac{C_{perchlorate,increased}}{C_{perchlorate,baseline}}\right)^{\beta}$$

And subsequently ΔTSH is:

$$\Delta TSH = \left(TSH_{baseline} \times \left(\frac{C_{perchlorate,increased}}{C_{perchlorate,baseline}}\right)^{\beta}\right) - TSH_{baseline}$$

Comparing Predicted Changes in fT4 and TSH from Steinmaus et al. (2016) to the BBDR Model Output

To compare the results of these analyses with the BBDR model it is necessary to estimate what the doses (µg/kg/day) used in the BBDR model would translate to in the context of urinary output (µg/L).

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This is because Steinmaus et al. (2016) estimated their regression equations using urinary concentrations of perchlorate, rather than perchlorate doses. Therefore to convert the BBDR doses to urinary concentrations, the BBDR perchlorate doses are multiplied by 74 kg[1] (U.S. EPA, 2011; Table 8-29), an assumed average body weight for a first trimester pregnant woman, to get estimates of daily urinary perchlorate output per day. Then, the estimated daily output (µg/d) was divided by the number of liters per day assumed excreted by the women in the study, which is assumed to be equal to 1.82 (L/day) (Moos et al., 2016). Further, the Steinmaus et al. (2016) fT4 equation has fT4 in units of ng/dL, so EPA converted the fT4 changes predicted by our equation to pmol/L to make them directly comparable to the output of the BBDR model. This units conversion used the relationship of 1 ng/dL = 12.87 pmol/L for fT4 (Quest Diagnostics, n.d.)

Given the log-linear and log-log relationships modeled in Steinmaus et al. (2016) for fT4 and TSH, respectively, it is the percent change in urinary perchlorate from a defined baseline that drives the results. For these analyses EPA assumed 0.1 µg/kg/day as the baseline perchlorate dose. This value is equivalent to a urinary concentration of approximately 4.1 µg/L, which is lower than the median perchlorate concentration in the Steinmaus et al. (2016) cohort (i.e., 6.50 µg/L) and slightly higher than the median perchlorate concentration from the 2001-2002 NHANES data cited by Steinmaus (i.e., 3.0 µg/L). The assumed baseline urinary value is important in this function, since the perchlorate impact is based upon its increase over baseline, i.e., a given dose level will have less impact if starting from a higher baseline when compared to results starting from a lower baseline (Steinmaus et al. 2016).

Further, given the log transformation of TSH it was also necessary to assume a baseline TSH level to evaluate the given change. For this analysis EPA assumed two baseline values to evaluate how this parameter may impact the results. EPA used both the baseline TSH level predicted by the BBDR model at 0.1 µg/kg/day perchlorate (1.40 mIU/L) and the median TSH level from Steinmaus et al. (1.20 mIU/L).

EPA has presented several different changes in perchlorate dose up to 4 µg/kg/day (0.1 to 4 µg/kg/day or 4.1 to 163 µg/L urinary perchlorate) and calculated the corresponding changes in fT4 and TSH. Given that the mean urinary iodine level for Steinmaus is 154.5, EPA initially compared results to the median iodine intake (170 µg/day) output from the BBDR model. Steinmaus et al. (2016) collected fT4 and TSH values at 15-20 weeks (though urinary perchlorate and iodine were collected at 7 weeks) therefore, EPA used GW 16 week BBDR model results for these analyses. Given the small changes being predicted by the BBDR model compared to the Steinmaus et al. (2016), EPA also evaluated the BBDR model's predicted changes in fT4 and TSH at an iodine intake of 75 µg/day.

Table B-3 shows changes in fT4 predicted by the Steinmaus et al. (2016) urinary perchlorate concentration-response relationship compared with changes in fT4 predicted by the BBDR model for median (170 µg/day) and low (75 µg/day) iodine intake. Figure B-1 describes the differences between

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[1] This was done to ensure accuracy in the presentation of the results. However, given the same body weight and daily urinary output is applied to all doses and the same percentage change occurs whether the input is a dose or an intake, the value used for this conversion does not impact the resulting predicted changes in fT4.

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these predicted fT4 changes in graphical form. Table B-4 shows changes in TSH predicted by the Steinmaus et al. (2016) perchlorate concentration-response relationship compared with changes in TSH predicted by the BBDR model for median (170 µg/day) and low (75 µg/day) iodine intake. Figure B-2 describes the differences between these predicted TSH changes in graphical form using the results from the Steinmaus analysis assuming a baseline TSH of 1.4 mIU/L based on the BBDR model output.

Table B-3. Change in fT4 Predicted by Steinmaus et al. (2016) Compared to Predicted Changes in fT4 from the BBDR Model for Median (170 µg/day) and low (75 µg/day) Iodine Intake

ΔPerchlorate Urinary Conc (µg/L) (Δ Dose; µg/kg/day)	Percent Increase In Perchlorate Dose	Steinmaus Predicted ΔfT4 (pmol/L) (Based on Central β and lower and upper 95% CI Estimates)[1]			BBDR Model Predicted ΔfT4 at GW 16 (pmol/L)	
		Lower Estimate	Central Estimate	Upper Estimate	I intake = 170 µg/day	I Intake = 75 µg/day
4.1 to 8 (0.1 to 0.2)	100%	-0.050	-0.205	-0.356	-0.001	-0.006
4.1 to 12 (0.1 to 0.3)	200%	-0.080	-0.325	-0.565	-0.001	-0.013
4.1 to 16 (0.1 to 0.4)	300%	-0.101	-0.411	-0.713	-0.002	-0.019
4.1 to 20 (0.1 to 0.5)	400%	-0.117	-0.477	-0.828	-0.003	-0.026
4.1 to 24 (0.1 to 0.6)	500%	-0.130	-0.531	-0.921	-0.003	-0.032
4.1 to 28 (0.1 to 0.7)	600%	-0.141	-0.576	-1.001	-0.004	-0.038
4.1 to 32.5 (0.1 to 0.8)	700%	-0.151	-0.616	-1.069	-0.005	-0.045
4.1 to 37 (0.1 to 0.9)	800%	-0.160	-0.651	-1.130	-0.005	-0.051
4.1 to 41 (0.1 to 1)	900%	-0.167	-0.682	-1.184	-0.006	-0.057
4.1 to 81 (0.1 to 2)	1900%	-0.218	-0.887	-1.540	-0.012	-0.118
4.1 to 122 (0.1 to 3)	2900%	-0.247	-1.008	-1.749	-0.019	-0.176
4.1 to 163 (0.1 to 4)	3900%	-0.268	-1.093	-1.897	-0.026	-0.232

[1] Calculated based on $\Delta fT4 = \beta \times \log_{10}\left(\frac{C_{perchlorate,increased}}{C_{perchlorate,baseline}}\right)$, with β = -0.053 (-0.092, -0.013), fT4 measured in ng/dL; result multiplied by 12.87 to obtain pmol/L result.

Table B-4. Change in TSH Predicted by Steinmaus Compared to Predicted Changes in TSH from the BBDR Model for Median (170 µg/day) and Low (75 µg/day) Iodine Intake

ΔPerchlorate Urinary Conc (µg/L) (Δ Dose; µg/kg/day)	Percent Increase In Perchlorate Dose	Steinmaus Predicted ΔTSH (mIU/L) (Based on Central β and lower and upper 95% CI Estimates)[1]						BBDR Model Predicted ΔTSH at GW 16[2] (mIU/L)	
		TSH Baseline[3] = 1.4 mIU/L			TSH Baseline[4] = 1.2 mIU/L				
		Lower Estimate	Central Estimate	Upper Estimate	Lower Estimate	Central Estimate	Upper Estimate	I intake = 170 µg/day	I Intake = 75 µg/day
4.1 to 8 (0.1 to 0.2)	100%	0.008	0.071	0.136	0.007	0.061	0.116	0.000	0.007
4.1 to 12 (0.1 to 0.3)	200%	0.012	0.114	0.221	0.011	0.097	0.189	0.000	0.014
4.1 to 16 (0.1 to 0.4)	300%	0.016	0.145	0.284	0.013	0.124	0.243	0.000	0.021
4.1 to 20 (0.1 to 0.5)	400%	0.018	0.170	0.335	0.016	0.145	0.286	0.000	0.029
4.1 to 24 (0.1 to 0.6)	500%	0.020	0.190	0.378	0.017	0.163	0.323	0.001	0.036
4.1 to 28 (0.1 to 0.7)	600%	0.022	0.208	0.415	0.019	0.178	0.354	0.001	0.043
4.1 to 32.5 (0.1 to 0.8)	700%	0.024	0.223	0.447	0.020	0.191	0.382	0.001	0.050
4.1 to 37 (0.1 to 0.9)	800%	0.025	0.237	0.476	0.021	0.203	0.407	0.001	0.058
4.1 to 41 (0.1 to 1)	900%	0.026	0.249	0.503	0.022	0.213	0.430	0.001	0.065
4.1 to 81 (0.1 to 2)	1900%	0.034	0.333	0.687	0.029	0.284	0.587	0.002	0.139

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ΔPerchlorate Urinary Conc (µg/L) (Δ Dose; µg/kg/day)	Percent Increase In Perchlorate Dose	Steinmaus Predicted ΔTSH (mIU/L) (Based on Central β and lower and upper 95% CI Estimates)[1]						BBDR Model Predicted ΔTSH at GW 16[2] (mIU/L)	
		TSH Baseline[3] = 1.4 mIU/L			TSH Baseline[4] = 1.2 mIU/L				
		Lower Estimate	Central Estimate	Upper Estimate	Lower Estimate	Central Estimate	Upper Estimate	I intake = 170 µg/day	I Intake = 75 µg/day
4.1 to 122 (0.1 to 3)	2900%	0.039	0.383	0.803	0.033	0.328	0.686	0.003	0.215
4.1 to 163 (0.1 to 4)	3900%	0.042	0.420	0.889	0.036	0.359	0.760	0.004	0.293

[1] Calculated based on $\Delta TSH = \left(TSH_{baseline} \times \left(\frac{C_{perchlorate,increased}}{C_{perchlorate,baseline}}\right)^{\beta}\right) - TSH_{baseline}$, with β = -0.071 (0.008, 0.133).

[2] Based on BBDR model results provided dated August 23, 2017.

[3] Based on BBDR Model TSH prediction at 0.1 µg/kg/day.

[4] Based on median TSH from Steinmaus et al. (2016).

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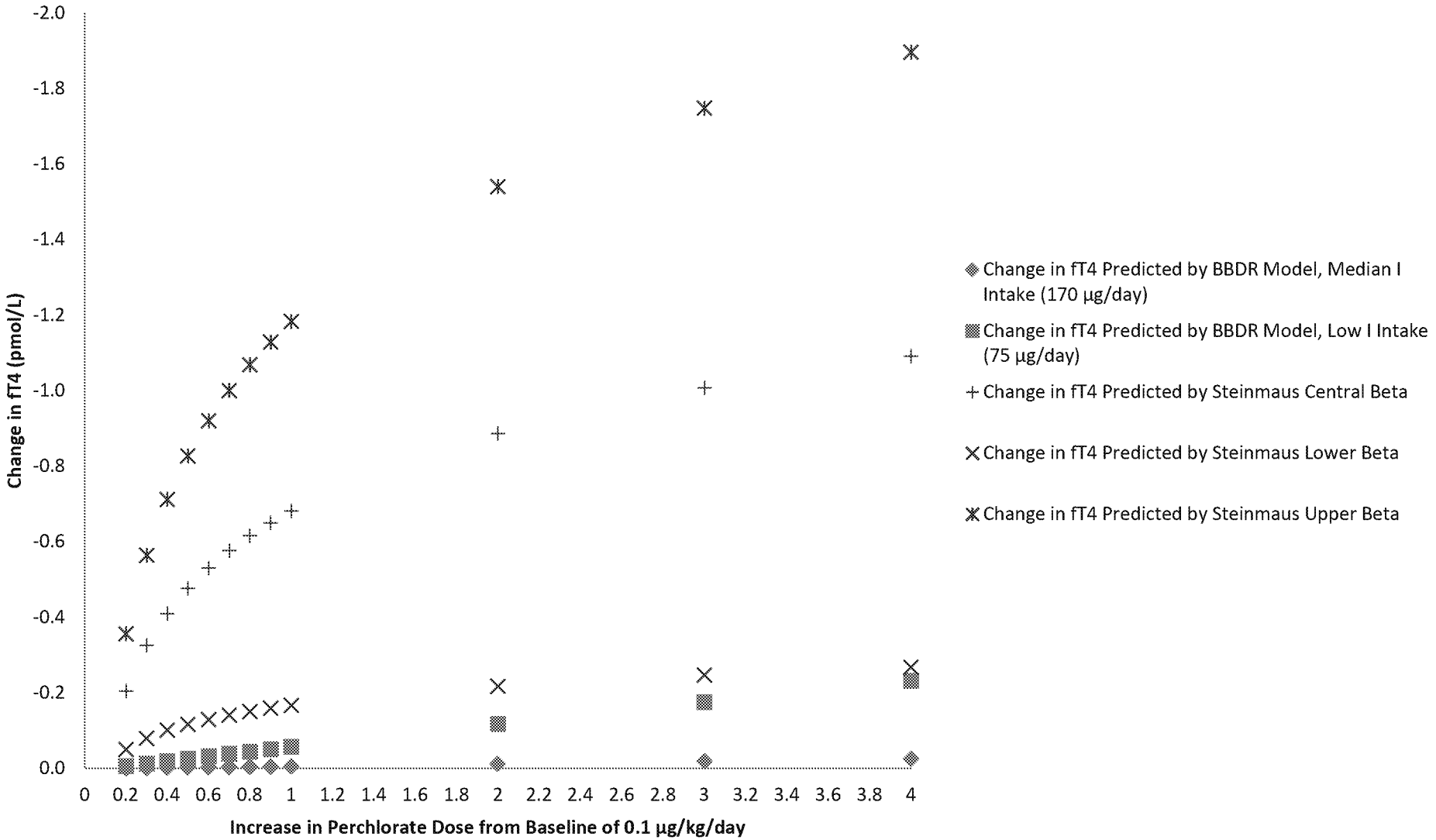
Figure B-1. Comparing Predicted fT4 Changes from the BBDR Model and Steinmaus et al. (2016) due to Changes in Perchlorate Dose[2]



[2] Analogous changes in urinary perchlorate presented in Table B-3.

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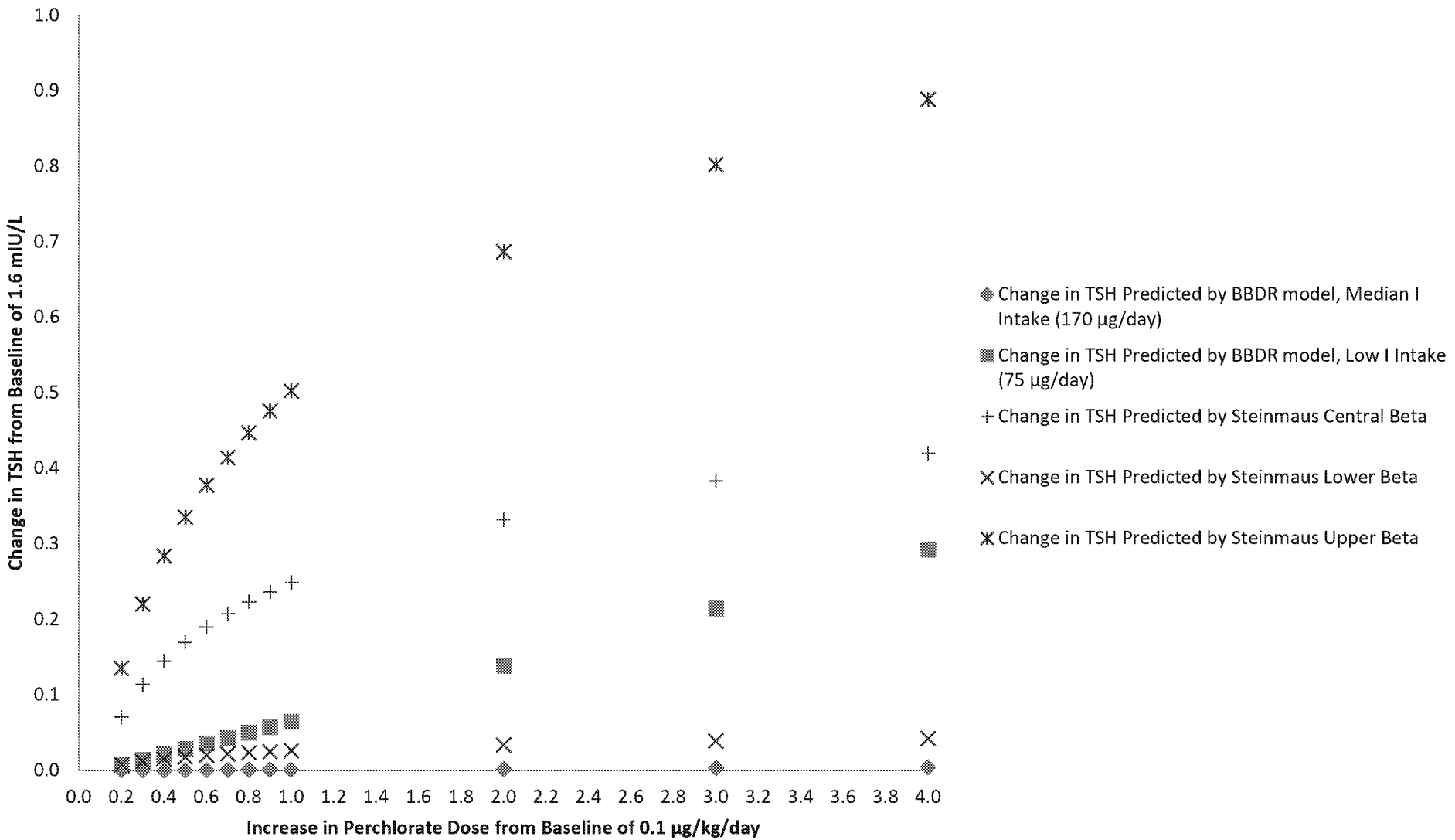
Figure B-2. Comparing Predicted TSH Changes from the BBDR Model and Steinmaus et al. (2016) due to Changes in Perchlorate Dose[3]



[3] Analogous changes in urinary perchlorate presented in Table B-4.

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Table B-3 and Figure B-1 show that in all instances the BBDR Model predicts a smaller change than that projected by the Steinmaus et al. (2016) beta slope. The closest match, especially at lower perchlorate doses, is between the low-iodine runs of the BBDR model and the low estimate of the Steinmaus et al. (2016) slope.

Table B-4 shows that the baseline TSH value does not have a large impact on the predicted changes in TSH due to changes in perchlorate when using the Steinmaus et al. (2016) function. This is likely because the two baseline values used were not very different from one another. Table B-4 also shows that when considering the median iodine intake, the changes predicted by the BBDR model for TSH are smaller than that predicted by Steinmaus et al. (2016), even when compared to the predictions based on the lower beta estimate from the 95% CI presented. However, when comparing the BBDR model's low-iodine TSH changes to those predicted by Steinmaus et al. (2016) they are closer in magnitude to the lower effect estimates and steadily increase to greater predicted changes as doses increase.

This analysis demonstrates that the relationships predicted by Steinmaus et al. (2016) show a steeper dose-response relationship between perchlorate exposure and decreases in fT4 than the BBDR model. However, the BBDR model's low iodine predictions for TSH shower a steeper dose response at higher perchlorate doses than the Steinmaus et al. (2016) lower effect estimates.

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Appendix C – An Approach to Assess Changes in IQ as a Result of Changes in Perchlorate Exposure Using Steinmaus et al. (2016)

In the current analysis to inform the derivation of an MCLG for perchlorate, EPA developed an approach which evaluates changes in neurodevelopmental outcomes (e.g. intelligence quotient (IQ)) for a given change in perchlorate through a two-step process. That is, perchlorate exposure is connected to changes in free thyroxine (fT4) using EPA's Biologically Based Dose Response (BBDR) Model and subsequently predicted changes in fT4 are linked to potential neurodevelopmental outcomes with the epidemiological literature. This is summarized in Figure C-3.

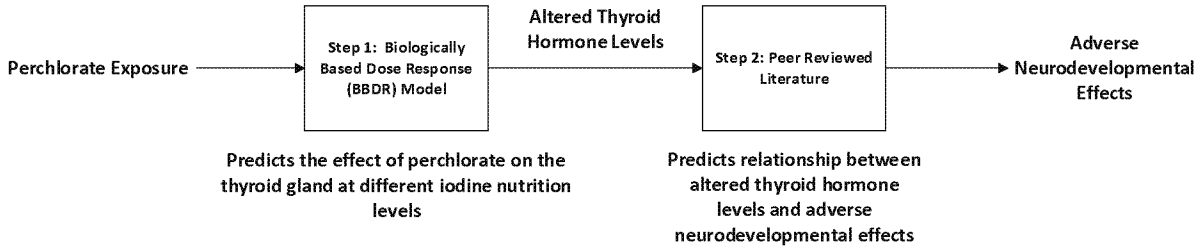

Figure C-3. Overview of Approach to Inform the Derivation of an MCLG for Perchlorate

To evaluate approach predictions, EPA used the epidemiological literature to connect both changes in perchlorate to fT4 and changes in fT4 to changes in neurodevelopment. That is, instead of using the BBDR model as described in Step 1 of

Figure **C-3**, this appendix describes an approach to evaluate the effect of perchlorate on fT4 using the epidemiologic literature. Specifically, an approach is presented to utilize a function reported by Steinmaus et al. (2016) that connects perchlorate exposure to changes in fT4 levels. While multiple epidemiological studies suggest a link between perchlorate exposure and changing thyroid hormone levels (e.g., Blount et al., 2006 and Steinmaus et al., 2013), Steinmaus et al. (2016) is the most appropriate study for this analysis because the study evaluated a large population of women with early pregnancy exposure to perchlorate and subsequent thyroid hormone impacts.

For Step 2 of Figure C-3, 5 studies (Finken et al., 2013; Korevaar et al., 2016; Pop et al., 1999, 2003; Vermiglio et al., 2004) were identified that connect fT4 levels to altered neurodevelopmental outcomes that can be used for further analysis to potential inform the derivation of the MCLG (See Section 5). For the purposes of this example, EPA used a derived relationship between fT4 and IQ from a *de novo* analysis of data presented in Korevaar et al. (2016), as presented in Section 5.3.2. This approach is summarized in Figure C-4. Subsequent sections will walk through each step and present results of this analysis.

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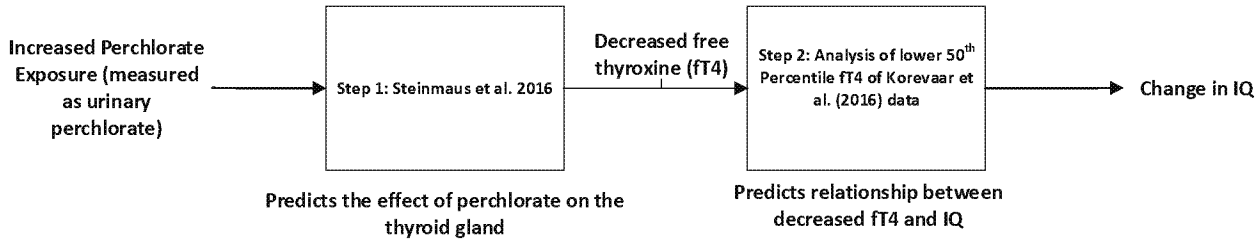

Figure C-4. Overview of Approach Presented in Appendix

Methods

Connect changes in Perchlorate to Changes in fT4

Appendix B describes how to use data presented in Steinmaus et al. (2016) to connect changes in perchlorate exposure to changes in fT4. In summary, the underlying function for the Steinmaus model most useful for EPA's purposes represents the dependence of fT4 on perchlorate exposure as a slope (β_s) of the change in fT4 per $\log_{10}$ change in perchlorate urinary concentration:

$$fT4 = \beta_s \times \left(\log_{10}\left(C_{perchlorate_0}\right)\right) + \beta_0 + \beta_{..}$$

Where:

β_s= Slope parameter (Table C-5) for $\log_{10}(C_{perchlorate_0})$

$C_{perchlorate_0}$ = the concentration of perchlorate in urine (µg/L)

β_0 = intercept

$\beta_{..}$ = parameters for all other covariates in the model[4]

Therefore, assuming the values of all covariates in the model are held constant, with the exception of urinary perchlorate, the change in fT4 (ΔfT4) due to a change in perchlorate can be estimated as:

$$\Delta fT4 = \beta_s \times \log_{10}\left(\frac{C_p}{C_b}\right)$$

Where:

β_s = Slope parameter (Table C-5)

[4] Covariates included urinary creatinine, maternal age, education level, ethnicity, gestational age at serum collection, and urinary thiocyanate (Steinmaus 2016)

C_b= the concentration of perchlorate in urine (µg/L) at an assumed baseline

C_p= the concentration of perchlorate in urine (µg/L) after an increase in exposure

As a result, the decreased fT4 value due to an increase in perchlorate ($fT4_p$) is simply ΔfT4 added to the baseline fT4 ($fT4_b$). That is:

$$fT4_p = fT4_b + \Delta fT4$$

Link Changes in fT4 to Changes in IQ

Section 5.3.2 and Section 6.2 describe how to use data presented in Korevaar et al. (2016) to connect changes in fT4 to changes in IQ, based on a *de novo* analysis of the lowest 50th percentile of fT4 from the Korevaar data. That is, to link a predicted change in IQ (ΔIQ) to a change in fT4, the multivariate beta estimate (β_k) will be used as it accounts for potential confounders in the relationship between fT4 and IQ. The resulting model to evaluate the change in IQ for a change in fT4 is:

$$\Delta IQ = \ln\left(\frac{fT4_p}{fT4_b}\right) \times \beta_k$$

Where:

β_k = slope parameter for ln(fT4 ratio) (Table C-5)

$fT4_p$= fT4 value with increased perchlorate exposure

$fT4_b$= fT4 value at baseline

Table C-5. Summary of Estimated Standard Errors for the Effect Estimates from Steinmaus et al. (2016) and Korevaar et al. (2016)

Study	Effect Estimate (slope parameter)	Effect Estimate Estimated Value	95% Confidence Interval	Derived Standard Error[a]
Steinmaus (2016)	β_s (per $\log_{10}$ unit change in urinary perchlorate (µg/L))	ng/dL: -0.053 pmol/L[b]: -0.682	-0.092 , -0.013 -1.18 , -0.167	0.020 ng/dL 0.259 pmol/L
Korevaar (2016)	β_k (per ln unit change in fT4 (pmol/L))	4.63[c]	(-0.52 , 9.78)	2.628

[a] Steinmaus (2016) did not report an estimate of SE of Beta(s) explicitly, they were derived the value from the reported CI on β_s. SE estimated by dividing the range of the 95% CI by 1.96 (the z-score) and also by 2 (to divide into the upper and lower tails). SE is necessary for Monte Carlo analysis which is described in the discussion below.

[b] Steinmaus et al. (2016) reported results in terms of ng/dL. EPA converted them to pmol/L according to pmol/L = ng/dL * 12.87

[c] Estimated based on de novo analysis of Korevaar et al. (2016)

Define Baseline Parameters

Each of the above steps requires a baseline value in order to estimate a change in the outcome of interest. In order to demonstrate the results of our analysis, baseline values were used that represent a

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potentially vulnerable population. That is these individuals have lower fT4 concentrations compared to the majority of the population and also lower perchlorate exposures. Specifically, it was assumed that this population has a baseline fT4 level of 7.72 pmol/L and baseline urinary perchlorate of 0.92 µg/L. Both values are based on the 10th percentile fT4 for non-pregnant women of child bearing based on NHANES data (2007-2012).[5]

Estimate Central and Upper Bound Changes in IQ

Given the goal of the MCLG is to estimate the concentration "at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety," central and upper bound resulting IQ losses are presented based on the central and lower bound effect estimates of Steinmaus et al. (2016) and the central effect estimate from our analysis of the Korevaar et al. (2016) data. Since the Steinmaus et al. (2016) regression of perchlorate on fT4 was a negative slope, using the lower bound on the slope predicts the greatest expected decrease in fT4, and subsequently the greatest predicted change in IQ. Further, by holding the fT4 to IQ effect estimate constant (i.e., not using bounding estimates), we are allowing for a more explicit evaluation of perchlorate effects without overlaying the uncertainty and variability embedded in the Korevaar et al. analysis of fT4 to IQ relationship.

Results

Results of the predicted IQ change assuming the NHANES 10th percentile fT4 and baseline urinary perchlorate are presented in Table C-6. In this table both the urinary perchlorate concentration and an associated dose of perchlorate with that urinary concentration are included in order to relate the BBDR model results to the results seen in this analysis. These estimated perchlorate doses were derived by multiplying urinary perchlorate levels measured in µg/L by an estimate of daily urine output of 1.45 L/day, which is consistent with the assumed daily urine output in the BBDR model, and dividing by 74 kg[6] (U.S. EPA, 2011; Table 8-29), which is an assumed average body weight for a first trimester pregnant woman. This yields estimated perchlorate dose figures measured in µg/kg/day.

Various changes in urinary perchlorate are presented, and the change which results in a 1 point change in IQ is bolded for both the central and largest predicted IQ changes.

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[5] Study population inclusion criteria included non-pregnant woman aged 20-44; Total T4 within the reference range of 6.1 µg/dL to 12.12 µg/dL; TSH within the reference range of 0.24 mcIU/mL to 5.60 mcIU/mL; Tg-Ab within the normal range of less than 4.0 IU/mL; TPO-Ab within the normal range of less than 0.9 IU/mL; no estrogen, androgen, or lithium supplements; no reported thyroid disease; and not currently on thyroid medication.

[6] This was done to ensure accuracy in the presentation of the results. However, given the same body weight and daily urinary output is applied to all doses and the same percentage change occurs whether the input is a dose or an intake, the value used for this conversion does not impact the resulting predicted changes in fT4 but it does impact the estimated dose associated with a given IQ change.

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Table C-6. Predicted Changes in fT4 and IQ Based on Central and Lower Effect Estimates from Steinmaus et al. (2016) and Central Effect Estimate from Korevaar et al. (2016)

Baseline Urinary Perchlorate (µg/L) (Dose; µg/kg/day)[a]	% Increase in Urinary Perchlorate	Increased Urinary Perchlorate (µg/L) (Dose; µg/kg/day)	Baseline fT4 (pmol/L)	Central Estimates of ΔfT4 and ΔIQ[b]			Upper Estimate of ΔfT4 and ΔIQ[c]		
				% Change in fT4	Decreased fT4 due to Perchlorate (pmol/L)	ΔIQ	% Change in fT4	Decreased fT4 due to Perchlorate (pmol/L)	ΔIQ
0.92 (0.02)	10%	1.02 (0.02)	7.72	-0.37%	7.69	-0.02	-0.63%	7.67	-0.03
	25%	1.16 (0.02)		-0.86%	7.65	-0.04	-1.49%	7.61	-0.07
	50%	1.39 (0.03)		-1.56%	7.60	-0.07	-2.70%	7.51	-0.13
	100%	1.85 (0.04)		-2.66%	7.51	-0.12	-4.62%	7.36	-0.22
	200%	2.77 (0.05)		-4.22%	7.39	-0.20	-7.32%	7.16	-0.35
	500%	5.54 (0.11)		-6.88%	7.19	-0.33	-11.93%	6.80	-0.59
	625%	6.70 (0.13)		-7.60%	7.13	-0.37	-13.20%	6.70	-0.66
	1,000%	10.16 (0.20)		-9.20%	7.01	-0.45	-15.97%	6.49	0.81
	1,725%	**16.86 (0.33)**		11.14%	6.86	-0.55	**-19.34%**	**6.23**	**-1.00**
	15,950%	**148.30 (2.91)**		**-19.49%**	**6.22**	**-1.00**	-33.83%	5.11	-1.91

[a] Estimated assuming a 74 kg woman with 1.45L/day urine output

[b] Estimated using the central effect estimates from Steinmaus et al. (2016) and our analysis of the Korevaar et al. (2016) data.

[c] Estimated using the lower effect estimate from Steinmaus et al. (2016), which predicts the greatest decrease in fT4 per unit of urinary perchlorate, and the central effect estimate from our analysis of the Korevaar et al. (2016) data.

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Discussion

Table C-6 demonstrates that approximately a 19% change in fT4 is needed to correspond to a 1 point change in IQ. In this current analysis, a 1 IQ point change was seen when urinary perchlorate increased between 1,725 to almost 16,000 percent. When considering the assumed baseline urinary perchlorate, this percent change is associated with approximately 17 to 148 μg/L perchlorate (0.33 to 2.91 μg/kg/day). 17 μg/L is between the 97.5th and 99th percentile of urinary perchlorate values for non-pregnant women of child bearing based on NHANES data (2007-2012).[5] 148 μg/L is greater than the 99th percentile of urinary perchlorate (22.1 μg/L) from NHANES (2007-2012).

The magnitude of the change in perchlorate exposure necessary to precipitate a 19% change in fT4 change depends on the assumed baseline urinary perchlorate concentration, the baseline fT4 concentration, and the effect estimate used to relate perchlorate exposure to fT4. There is also additional uncertainty that exists around the true relationship between fT4 and IQ. This uncertainty is not demonstrated in the main analysis, which is specifically evaluating how varying the relationship between perchlorate and fT4 can impact predicted changes in IQ. To explore also how varying the relationship between fT4 and IQ may impact the relationship between perchlorate and IQ, EPA conducted a Monte Carlo analysis.

For this additional analysis, we used the Monte Carlo method, with alternative values of the parameters β_s and β_k randomly chosen from a normal distribution, with mean values and standard errors indicated by their respective reported central estimates and 95% CI (Table C-5). It was assumed the two parameter values for β_s and β_k are statistically independent (i.e., there was a separate random number generator for each distribution). The greatest change limit on ΔIQ was defined as the 97.5% quantile of 100,000 iterations of the calculation. The results of this Monte Carlo analysis are presented in Table C-7, given the need to protect the most sensitive population for the purposes of informing the derivation of an MCLG, only the central and upper bound estimates from the Monte Carlo analysis are presented.

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Table C-7. Predicted Central and Upper Estimated IQ Change Due to Increased Doses of Perchlorate Assuming Baseline Parameters for a Vulnerable Population Based on a Monte Carlo Analysis with Variable Values for Effects Estimates β_s and β_k

Baseline Urinary Perchlorate (µg/L) (Dose; µg/kg/day)[a]	% Increase in Urinary Perchlorate	Increased Urinary Perchlorate (µg/L) (Dose; µg/kg/day)	Baseline fT4 (pmol/L)	Central Estimates of ΔfT4 and ΔIQ[b]			Upper Estimate of ΔfT4 and ΔIQ[c]		
				% Change in fT4	Decreased fT4 due to Perchlorate (pmol/L)	ΔIQ	% Change in fT4	Decreased fT4 due to Perchlorate (pmol/L)	ΔIQ
0.92 (0.02)	10%	1.02 (0.02)	7.72	-0.37%	7.69	-0.02	-0.64%	7.67	-0.05
	25%	1.16 (0.02)		-0.86%	7.65	-0.04	-1.49%	7.60	-0.11
	50%	1.39 (0.03)		-1.56%	7.60	-0.07	-2.72%	7.51	-0.19
	100%	1.85 (0.04)		-2.66%	7.51	-0.12	-4.64%	7.36	-0.33
	200%	2.77 (0.05)		-4.22%	7.39	-0.20	-7.36%	7.15	-0.54
	500%	5.54 (0.11)		-6.88%	7.19	-0.33	-12.00%	6.79	-0.89
	625%	**6.70 (0.13)**		-7.60%	7.13	-0.37	**-13.27%**	**6.70**	**-0.99**
	1,000%	10.16 (0.20)		-9.20%	7.01	-0.45	-16.06%	6.48	-1.22
	1,725%	16.86 (0.33)		-11.14%	6.86	-0.55	-19.45%	6.22	-1.50
	15,950%	**148.30 (2.91)**		**-19.49%**	**6.22**	**-1.00**	-34.01%	5.09	-2.84

[a] Estimated assuming a 74 kg woman with 1.45L/day urine output

[b] Central point estimates based on the direct algebraic solutions to the combined linear models using the central beta estimates from each analysis

[c] Upper bound from the 95th percentile of Monte Carlo distribution of results in which β_s and β_k were variable according to an assumed normal distribution and 100,000 iterations

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Table C-7 demonstrates that the greatest estimate of ΔIQ results when introducing uncertainty around both the β_s and β_k estimates. Including the additional uncertainty regarding the relationship between fT4 and IQ changes the upper bound estimate of the change in perchlorate needed to precipitate a 1 IQ point change, even while assuming the same level of background urinary perchlorate and baseline fT4. This is demonstrated by evaluating the amount of perchlorate needed to result in a one point change in Table C-6 and Table C-7. Specifically, when only considering the central estimate of β_k and the lower estimate of β_s (i.e., the greatest predicted decrease in fT4 for a given perchlorate exposure), the smallest predicted increase in urinary perchlorate needed to result in a 1 point reduction in IQ was 1,725%, or a change in urinary perchlorate from 0.92 μg/L to 16.86 μg/L (0.02 μg/kg/day to 0.33 μg/kg/day). However, the Monte Carlo analysis that includes uncertainty around β_k predicts a 1 point reduction in IQ from a 625% increase in urinary perchlorate, or a change in urinary perchlorate from 0.92 μg/L to 6.7 μg/L (0.02 μg/kg/day to 0.13 μg/kg/day).

Given all the variables that can impact the resulting urinary perchlorate value, which could result in a given change in IQ, additional Monte Carlo analysis using a different set of background levels of fT4 and urinary perchlorate was conducted. For this alternative background scenario the median fT4 and urinary perchlorate values presented in Steinmaus et al. (2016) were utilized. Specifically, a baseline fT4 of 10.94 pmol/L was assumed along with a baseline urinary perchlorate value of 6.50 μg/L. Both values are based on the median value for each parameter from Steinmaus et al. (2016). The authors note that the median urinary perchlorate of 6.50 μg/L is relatively high compared to what has been observed from other sources. The results of this alternative baseline scenario are presented in Table C-8.

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Table C-8. Predicted Central and Upper Estimated IQ Change Due to Increased Doses of Perchlorate, Assuming Baseline Parameters for the Steinmaus et al. (2016) Population Based on a Monte Carlo Analysis With Variable Values for β_s and β_k

Baseline Urinary Perchlorate (µg/L) (Dose; µg/kg/day)[a]	% Increase in Urinary Perchlorate	Increased Urinary Perchlorate (µg/L) (Dose; µg/kg/day)	Baseline fT4 (pmol/L)	Central Estimates of ΔfT4 and ΔIQ[b]			Upper Estimate of ΔfT4 and ΔIQ[c]		
				% Change in fT4	Decreased fT4 due to Perchlorate (pmol/L)	ΔIQ	% Change in fT4	Decreased fT4 due to Perchlorate (pmol/L)	ΔIQ
6.50 (0.13)	10%	7.15 (0.14)	10.94	-0.26%	10.91	-0.01	-0.45%	10.89	-0.03
	25%	8.12 (0.16)		-0.60%	10.87	-0.03	-1.05%	10.82	-0.07
	50%	9.75 (0.19)		-1.10%	10.82	-0.05	-1.92%	10.73	-0.14
	100%	13.00 (0.25)		-1.88%	10.73	-0.09	-3.28%	10.58	-0.23
	200%	19.50 (0.38)		-2.97%	10.61	-0.14	-5.19%	10.37	-0.38
	500%	39.00 (0.76)		-4.85%	10.41	-0.23	-8.47%	10.01	-0.62
	1,000%	71.50 (1.40)		-6.49%	10.23	-0.31	-11.33%	9.70	-0.84
	1,650%	**113.75 (2.23)**		-7.75%	10.09	-0.37	**-13.53%**	**9.46**	**-1.02**
	130,000%	**8,456.50 (165.70)**		**-19.42%**	**8.82**	**-1.00**	-33.89%	7.23	-2.83

[a] Central point estimates based on the direct algebraic solutions to the combined linear models using the central beta estimates from each analysis

[b] Estimated assuming a 74 kg woman with 1.45L/day urine output

[c] Upper bound from the 95% Confidence Interval Estimated Using the Monte Carlo method on β_s and β_k, assumed normal distribution and 100,000 iterations

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The results in Table C-7 and Table C-8 demonstrate that a reduction in fT4 in the approximate range of 8% to 19% results in a 1 IQ point change, depending on whether the evaluation of the Korevaar-based distribution is at the upper bound or central estimate results, respectively. Further comparing Table C-7 and Table C-8 demonstrates if starting with a higher baseline fT4 level, a greater unit change is needed to see an equivalent percent change in IQ. This is because both the relationship between urinary perchlorate and fT4, and fT4 and IQ, are logarithmic regression slopes. This means that one does not get the same unit change in the dependent variable (i.e., fT4 or IQ) per change in the independent variable (e.g., perchlorate dose) when evaluating the function at different starting points. Thus, the change in perchlorate dose needed for a one unit change in IQ is much bigger if the baseline perchlorate is from the population median in Steinmaus et al. (6.5 ug/L urinary concentration) than if from the 10th percentile of the NHANES distribution (0.92 ug/L).

The results demonstrate this very clearly. That is, when evaluating the scenario representing a vulnerable population (baseline urinary perchlorate = 0.92 µg/L (0.02 µg/kg/day); baseline fT4 = 7.72) a 1 point change in IQ is predicted to occur when urinary perchlorate increases to between 6.7 µg/L (0.131 µg/kg/day) to 144.1 µg/L (2.82 µg/kg/day) when evaluating the central and lower estimates from Table C-7. When evaluating the scenario in which the Steinmaus et al. (2016) population median values are used (baseline urinary perchlorate = 6.50 µg/L (0.13 µg/kg/day); baseline fT4 = 10.94 pmol/L) a 1 IQ point change is predicted to occur when urinary perchlorate increases to between 113.75 µg/L (2.23 µg/kg/day) to 8,456.50 (165.70 µg/kg/day), or a 1,650 to 130,000 percent increase in urinary perchlorate.

This appendix demonstrates the wide range of urinary perchlorate values associated with a 1 unit IQ change. However, in informing the derivation of an MCLG for perchlorate, which aims to protect the most vulnerable, it is likely most appropriate to assume baseline values similar to those presented in Table C-6 and Table C-7, as opposed to Table C-8. Applying the Steinmaus et al. (2016) slope to the lower baseline perchlorate urinary concentration is reasonable given that the Steinmaus regression covers a California population whose minimum perchlorate urinary concentration was 0.23 µg/L (Steinmaus et al. 2016, Table 1), and thus is generalizable to the lower baseline perchlorate concentration of 0.92 µg/L. Furthermore, Blount et al. (2006) also found significant effects in regressions of perchlorate on thyroid hormone status (lower total T4 and elevated TSH) in a national sample that had an even lower baseline perchlorate (urinary geometric mean = 2.84 ug/L) than that of Steinmaus et al. (2016), which further suggests that the lower baseline perchlorate assumption is valid.

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Appendix D – Overview of Group 3 Studies

Cusick and Georgieff (2016): In this review paper, the role of nutrition in early brain development was examined with sufficient protein, long-chain polyunsaturated fatty acids, iron, zinc, and iodine during the first 3 years of life. The authors suggest that as iodine supports thyroid hormone synthesis, the fetal brain is most susceptible to iodine deficiency during the first trimester of pregnancy when fetal triiodothyronine production depends on maternal thyroxine. Thus, severe iodine deficiency can result in speech, hearing, and IQ deficits.

Dosiou and Medici (2017): In this review, the authors investigate the risk of child neurodevelopment with maternal hypothyroxinemia. The authors indicate a number of studies that have associated maternal hypothyroxinemia and adverse neurodevelopmental outcomes, but suggest that additional research is needed to elucidate its causes and potential long-term consequences.

Furnica et al. (2015): This study explores the biochemical criteria used to define maternal hypothyroxinemia and discuss potential maternal and fetal outcomes. Isolated hypothyroxinemia is defined as normal maternal TSH and fT4 levels in the lower 5th or 10th percentile of the pregnancy-related reference range. The definition and impacts of this condition are controversial due to the questionable performance of fT4 assays and the lack of studies that follow neurobehavioral performance of offspring in the long-term. Changes in brain development from maternal hypothyroxinemia are thought to be irreversible.

Gutleb et al. (2016): In their review, Gutleb et al.(2016) explore the impact of endocrine disruptors, such as perchlorate, on the thyroid hormone system. Chemicals that interfere with thyroid hormone homeostasis can impact brain development, energy metabolism, and reproduction. The authors discuss how perchlorate blocks the sodium-iodide symporter, thus preventing iodide uptake from the bloodstream and therefore the formation of thyroid hormones.

Haddow et al. (1999): TSH levels in second-trimester pre-natal serum samples were tested to identify pregnant women from New England with hypothyroidism. Each woman (15 with TSH concentrations between the 98th and 99.6th percentiles, and 47 with TSH concentrations at or above the 99.7th percentile) was matched with two randomly selected control subjects with TSH levels in the normal range based on criteria such as age at delivery. Offspring were tested 7 to 9 years after birth using the WISC-III to measure IQ. The average full-scale IQ of children of women who did not receive treatment for hypothyroidism during pregnancy was significantly less than the control group ($p = 0.005$).

Hamza, Hewedi, and Sallam (2013): 50 autistic Egyptian children, along with 50 controls, were assessed for severity of autism and IQ. Thyroid hormone levels were measured in the children as well as in their mothers, though not during pregnancy. Results suggested that there is a positive correlation between fT4 levels and IQ. The relationship between autism, IQ, and iodine deficiency was also evaluated.

Hollanders et al. (2015): IQ and motor function were assessed in 398 19-year-olds born very pre-term (< 32 weeks) or with very low birthweights (< 1,500 g). In this group, 120 individuals had experienced transient hypothyroxinemia of prematurity (THoP), a condition characterized by a temporary reduction in T4 that lasts 6 to 8 weeks with normal TSH levels. Specifically, THoP was

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defined as total T4 concentration less than three standard deviations below the daily mean (~60 nmol/L). No associations between THoP and IQ or motor function at age 19 years were found.

Hollanders et al. (Hollanders et al.): As a follow-up to Hollanders et al. (2015), Hollanders et al. (2016) examined THoP and problem behavior in young adults. Four hundred sixty-eight subjects born very preterm (< 32 weeks) or with very low birth weights (< 1,500 g), of whom 123 had THoP, were included. THoP was again defined as a T4 concentration less than three standard deviations below the daily mean (~60 nmol/L). At age 19, behavior was assessed with the Young Adult Self Report and Young Adult Behavioral Checklist for parents. THoP was associated with a 1.8 (95% CI: 1.01, 3.4)-fold increase in self-reported internalizing behavior, along with a 1.9 (95% CI: 1.1, 3.1)-fold increase in parent-reported total problem behavior.

Hoshiko, Grether, Windham, Smith, and Fessel (2011): Two different studies from California were examined by Hoshiko et al. The first group was comprised of 244 cases and 266 specifically from the San Francisco area, whereas the second group included 310 cases and 518 controls from across the state. In both groups, cases were identified as having autism spectrum disorder around 5 to 6 years of age. The authors relied on a database of T4 levels in newborns (measured within 24 hours of birth) as part of congenital hypothyroidism screening to provide estimates of thyroid hormone levels. Results indicated that low levels (OR = 2.74) of neonatal T4 were significantly associated with an increased risk of ASD.

Korzeniewski et al. (2013): 177 newborns with low birthweight from New Jersey were tested for thyroxine levels. At age 21, the participants were tested for autism spectrum disorder. Thyroxine z-scores less than -2.6, defined as transient hypothyroxinemia of prematurity, were associated with a greater risk for ASD, but not statistically significantly so.

Lyall et al. (2016): T4 and/or TSH levels were measured using newborn blood spots collected following 447,059 singleton births from 1996 and 446,424 from 2002 in the state of California. Mean levels of T4 and TSH were compared between ASD cases and non-cases. In the 1996 group, there were 1,876 cases of ASD, while there were 2,942 cases in the 2002 group. Although no significant association was observed for TSH levels and ASD in crude or adjusted analyses, there was a significant association among neonates with blood draw more than 48 hours from birth (adjusted risk ratio = 1.67, 95% CI: 1.08, 1.60) and T4 levels. These results suggest that newborns with the lowest T4 levels may have a modestly increased risk of developing ASD.

Man, Brown, and Serunian (1991): Serum butanol-extractable iodine (BEI) levels in 1,349 pregnant women from New England were measured before and after 24 gestational weeks to determine if they were hypothyroxinemic. Of those who were hypothyroxinemic, 15 were placed on adequate thyroid hormone replacement therapy and 21 were not treated; 210 euthyroid women served as the control group. Psychological examinations of the offspring were conducted at 8 months and 7 years using the Bayley Scales and IQ. On both tests, scores of the progeny from inadequately treated mothers were significantly lower ($p < 0.05$ for IQ; not reported for Bayley Scales).

Min et al. (2016): Maternal hypothyroxinemia can lead to neurodevelopmental effects in the developing fetus. This condition is characterized by low fT4 levels (< 5th or < 10th percentile) and normal TSH levels during pregnancy. In this review paper, the factors that lead to maternal hypothyroxinemia, including mild iodine deficiency, endocrine disruptors, or thyroid diseases, are discussed. The literature demonstrates that maternal hypothyroxinemia can negatively impact fetal

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brain development, resulting in cognitive deficits. Mothers must have adequate levels of fT4 to support normal brain development of their children.

Pearce (2015): In a review of Modesto et al. (2015), TSH, fT4, and TPO Ab were measured in the first trimester of 3,873 pregnant women in Finland. Maternal hypothyroxinemia was defined as serum TSH 0.1 to 2.5 mIU/L with fT4 below the 5th percentile (< 0.85 ng/dL). Mothers completed the Conners' Parent Rating Scale-Revised Short Form when their children were 8 years of age. Children of mothers with hypothyroxinemia were more likely to have ADHD scores 7% higher (95% CI: 3, 15) than children of euthyroid mothers. Excluding TPO Ab-positive mothers, those taking thyroid medications, or those with thyroid function assessed after the first trimester did not significantly change results.

Pérez-Lobato et al. (2014): The neurodevelopment of 300 Spanish children 9 to 11 years of age was assessed using a variety of test batteries. TSH and fT4 levels were also evaluated in the children. Results found that children with higher fT4 levels had higher odds of performing well on various test endpoints.

Pharoah, Connolly, Ekins, and Harding (1984): T3 and T4 levels were sampled during pregnancy (specific trimester evaluated is unclear) from 20 women with severe iodine deficiency in pre-literate society living in Papua New Guinea. The motor skills and intelligence of their offspring were later tested around 11 years of age. A significant relationship was observed between T4 levels and scores on all tests.

Scratch et al. (2014): Post-natal concentrations of fT4 were measured shortly after birth in 83 very pre-term infants born in Australia. Neurodevelopment was later assessed at 7 years of age using a variety of test batteries. Results indicated that lower fT4 levels were significantly associated with improved performance on some of the test batteries.

Soldin et al. (2002): Neonatal levels of T4 were analyzed for 52 children diagnosed with ADHD and matched controls. Samples were collected within 72 hours of birth. Children were diagnosed between 5.5 and 12 years of age, and controls were born in the same hospital and tested on the same day as their matches. Diagnoses were determined using full psychiatric interviews and supplemental interviews and questionnaires. There was no statistically significant relationship between T4 levels and the odds of ADHD diagnosis.

Soldin, Lai, Lamm, and Mosee (2003): Neonatal levels of T4 were analyzed for 52 children diagnosed with neurobehavioral disorders such as ADHD and autism, and matched controls. Samples were collected within 72 hours of birth. Children were diagnosed between 5.5 and 12 years of age, and controls were born in the same hospital and tested on the same day as their matches. Diagnoses were determined using full psychiatric interviews and supplemental interviews and questionnaires. There was no statistically significant relationship between T4 levels and the odds of disorder diagnosis.

Tiemeier and Korevaar (2016): Gyllenberg et al. (2016), a study linking schizophrenia to maternal hypothyroxinemia, was examined by Tiemeier and Korevaar. The cohort included 1,010 subjects with schizophrenia and 1,010 control subjects. Given that neurodevelopmental processes are regulated by thyroid hormone-dependent genes, the findings of the study were biologically plausible.

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F. Williams et al. (2012): Cord and post-natal T4, fT4, and TSH levels were evaluated in 662 Scottish women with premature deliveries (≤ 34 GW) and their offspring as part of the Millennium Study. At 5.5 years of age, the children were assessed for neurodevelopment using the McCarthy Scales. The results were opposite of what was expected, as mild hypothyroxinemia and lower maternal fT4 levels were associated with increased scores on the general cognitive index and the quantitative subscale of the McCarthy Scales.

F. Williams et al. (2013): Cord T4 levels were measured in 97 pregnant women from Scotland in the first trimester and at delivery as part of the Millennium Study. Neurodevelopment in the offspring was measured using the McCarthy Scales at 5.5 years. After adjusting for confounders, lower T4 levels were associated with improved scores on several aspects of the McCarthy Scales, although no data are presented on the measured levels of T4 in the population.

Willoughby (2011): 79 children between 9 and 14 years old were evaluated in a clinical neuropsychological experiment. Twenty-six of the children had congenital hypothyroidism, 23 had mothers who were hypothyroid during pregnancy, and 30 served as controls. In the experiments, controls performed significantly better at recalling episodic details.

Willoughby, McAndrews, and Rovet (2014): 54 children between 9 and 12 years of age were evaluated with a battery of memory tests. The hippocampal volume was also measured using MRI scans. Twenty-four of the children had mothers with hypothyroidism during pregnancy, and the other 30 served as controls. Maternal TSH and fT4 levels were measured in each trimester. Some of the memory test endpoints were significantly associated with maternal hypothyroidism, but most were not significant. Hippocampal volume was found to be correlated with thyroid hormone levels in the third trimester.

Wong et al. (2016): Wong et al. reviewed the literature to examine the predictive validity of developmental assessment performed between the ages of 1 and 3 years for school-age cognitive deficit in children born very preterm (≤ 32 weeks) or very low birthweight (< 1,500 g). In total, 24 studies (n = 3,133 children) administered the Bayley Scales of Infant Development or Griffiths Mental Development Scales (between ages 18 to 40 months). Various cognitive tests between ages 5 to 18 years were also included in this analysis. A pooled analysis revealed that 55% (95% CI: 45.7%, 63.89%) of children who might have cognitive difficulties in school were considered to have normal neurodevelopmental function at age 1 to 3 years.

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Appendix E – Overview of Group 2 Studies

Berbel et al. (2009): 104 pregnant Spanish women were split into three groups based on fT4 levels and hypothyroxinemia status, defined as the lowest 10th percentile (< 10.55 pmol/L). Group 1 received daily iodine supplements beginning at 4 to 6 GW. Group 2 received daily iodine supplements beginning at 12 to 14 GW, and Group 3 did not enroll until full-term and therefore did not receive supplements during gestation. Roughly 30% of participants in Groups 1 and 2 were hypothyroxinemic at the beginning of supplementation, but none were at term. Of Group 3 participants, 27% were hypothyroxinemic at term. The Brunet-Lezine scale was used to evaluate all offspring at 18 months. Results indicated that the mean development quotient, gross motor coordination, and fine motor coordination in Group 1 were significantly greater than both Group 2 and Group 3. The results suggest that the timing of iodine supplementation of hypothyroxinemic women during pregnancy may be associated with impaired neurodevelopment in offspring.

Costeira et al. (2011): 86 Portuguese women from an iodine-deficient region were assessed for thyroid hormone levels (total T4, fT4, and total T3) during all three trimesters. Offspring were evaluated for development using the Bayley Scales at 12, 18, and 24 months. Children at 18 and 24 months who were born to mothers with fT4 below the 10th percentile in the first trimester had lower psychomotor development scores compared to controls (-13.6 points lower PDI score in hypothyroxinemic group at 24 months, $p < 0.05$). Overall, first-trimester hypothyroxinemia was associated with increased odds for having a child with mildly or significantly delayed neurodevelopment (OR = 2.1, 95% CI not provided).

Craig et al. (2012): TSH and fT4 levels were measured during the second trimester for 98 hypothyroxinemic pregnant women and 98 controls living in Maine. Their offspring were assessed using the Bayley Scales at 2 years of age. Unadjusted scores on the Bayley Scale III were lower at 2 years of age in children born to mothers with low fT4 in the second trimester (17 gestational weeks) as compared to children born to mothers with normal fT4 levels (10th to 90th percentile, or 12.9 to 17.2 pmol/L). After adjustment for confounding variables differences were diminished, but 10th percentile fT4 levels was still associated with lower scores on the Bayley Scale (MDI score -1.4 (95% CI: -4.9, 2.0) points lower in hypothyroxinemic group; PDI score -1.9 (95% CI: -6.1, 2.4) points lower in hypothyroxinemic group).

Fan and Wu (2016): A meta-analysis including six studies (Craig et al., 2012; Ghassabian, Marroun, et al., 2014; Haddow et al., 1999; Y. Li et al., 2010; Pop et al., 2003; Smit et al., 2000) and a total of 4,449 participants was conducted to explore the relationship between maternal thyroid dysfunction and neuropsychological development of offspring. On average, the intelligence score of children whose mothers had thyroid abnormalities during pregnancy was 6.27 points (95% CI: -8.41, -4.13; $p < 0.001$) lower than that of children whose mothers had euthyroidism. With respect to motor scores, children in the thyroid abnormalities group had mean motor scores 5.99 points (95% CI: -9.42, -2.57; $p = 0.001$) lower than controls.

Ghassabian, Henrichs, and Tiemeier (2014): 3,903 pregnant women were tested for maternal levels of fT4, TSH, and TPO Ab during the first trimester as part of the Generation R study in the Netherlands. Severe hypothyroxinemia was defined as fT4 levels in the lowest 5th percentile. The main assessments offspring of hypothyroxinemic mothers were tested for included ADHD-associated symptoms at 6 years of age using the Child Behavior Checklist for Toddlers; expressive language skills at 1.5 years, 2.5 years, and 4 years using an age-appropriate short form of the MacArthur

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Communicative Development Inventory; and fetal and infant head growth using ultrasound and physical exams (respectively). Results from tests of ADHD-associated symptoms indicated that maternal hypothyroxinemia was associated with childhood ADHD after adjusting for factors related to the children, such as birthweight. However, the significance attenuated after adjusting for maternal factors such as education level ($\beta = 0.12$, 95% CI: -0.04, 0.27, $p = 0.14$). Mild and severe hypothyroxinemia before 18 GW were significantly associated with child expressive language delay at 1.5 and 2.5 years (mild hypothyroxinemia, OR = 1.44, 95% CI: 1.09, 1.91, $p = 0.01$; severe hypothyroxinemia, OR = 1.80, 95% CI: 1.24, 2.61, $p = 0.002$). Generally, pregnant women with mild hypothyroxinemia had large fetal head circumferences compared to a reference group.

Grau et al. (2015): TSH, fT4, and fT3 values were measured at the end of the first trimester in a group of Spanish women. At 1 year, 455 of the children were evaluated for neurodevelopment using the Brunet-Lezine scale, and 289 of those children were later evaluated using the WISC-IV test between 6 and 8 years of age. Participants were divided into subgroups based on urinary iodide concentrations and fT4 levels; one of the groups was characterized by fT4 levels below the 10th percentile. At 1 year of age they found that the children born to a hypothyroxinemic mother scored lower on almost all of the scales assessed by the Brunet-Lezine scale (e.g., postural control, coordination/oculomotor, sociability), but the differences were small and not statistically significant. When assessing IQ, children born to hypothyroxinemic women actually performed better on most scales, but the differences again were small and not statistically significant.

Júlvez et al. (2013): fT4 and TSH levels were evaluated in a population of 1,643 Spanish women prior to 21 GW. Around 14 months, offspring were evaluated using the Bayley Scales for mental and psychomotor development. Results of the analysis found that with decreasing fT4 there was also a decrease in MDI (p for trend = 0.03). fT4 was also found to have a directly proportional relationship with PDI, but not statistically significantly so (p for trend = 0.77)

Kooistra, Crawford, van Baar, Brouwers, and Pop (2006): Maternal levels of fT4 and TSH were evaluated in 108 Dutch women with fT4 concentrations in the lowest 10th percentile (< 10.4 pmol/L), as well as 96 Dutch women with fT4 levels between the 50th and 90th percentiles to serve as a control group. Thyroid hormone levels were measured at 12, 24, and 32 GW. The Neonatal Behavioral Assessment Scale, which includes endpoints such as motor maturity, orientation, and total reflexes, was used to evaluate newborns 3 weeks after birth. Having fT4 in the lowest 10th percentile was determined to be a predictor of lower orientation scores ($\beta = 0.173$, $p = 0.024$).

Li et al. (2010): Thyroid hormone levels were measured in 1,268 Chinese women between 16 and 20 GW, including TSH, total T4, fT4, and TPO Ab. In this study, hypothyroxinemia was defined as total T4 < 101.79 nmol/L with normal TSH and fT4, and negative TPO Ab. A group of 19 mother-child pairs was selected as the hypothyroxinemia case group, with a control group of 38 that are matched based on various characteristics such as birthweight. Offspring were evaluated using the Bayley Scales for MDI and PDI between 25 and 30 months of age. Among the hypothyroxinemic group, mean MDI and PDI scores were significantly lower than the control group (-9.3 points lower MDI score in hypothyroxinemic group, p = 0.004; -7.6 points lower PDI score in hypothyroxinemic group; $p < 0.007$).

Päkkilä et al. (2014): TSH, fT4, and TPO Ab were measured in first-trimester samples from 5,131 pregnant women in Finland. Their offspring were evaluated at 8 years of age for ADHD using the Rutter scale. A weak but significant association between high TSH levels and ADHD symptoms was

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observed, with slightly increased odds among girls. No association was observed for fT4 or TPO Ab and ADHD.

Päkkilä et al. (2015): Thyrotropin, fT4, and thyroid peroxidase antibodies were measured in 5,791 pregnant women in Finland. Performance of their children (n = 5,829) was evaluated by their teachers at 8 years of age and by themselves at 16 years of age. Healthcare records were examined for data on severe intellectual deficiency and mild cognitive limitation. Poorer scholastic performance in children was significantly associated with maternal thyroid dysfunction. Specifically, girls of mothers with subclinical hypothyroidism had more difficulties in mathematics than girls of euthyroid mothers (OR=1.62; 95% CI: 1.06-2.49). In addition, boys of hypothyroxinemic mothers repeated a class more often than boys of euthyroid mothers (OR=5.46; 95% CI: 1.19-25.06).

Suárez-Rodríguez, Julián, and Aguilar (2012): Maternal thyroid hormone levels were sampled at 37 GW from a group of Spanish women. Hypothyroxinemia was defined as fT4 levels in the lowest 10th percentile (< 9.5 pmol/L). Using the McCarthy Scales, 70 of the offspring were evaluated for neurodevelopment between 38 and 60 months of age. When comparing individuals born to mothers with and without hypothyroxinemia, children born to mothers with maternal hypothyroxinemia had lower performance on all subscales with general cognitive index (mean score fT4>10th percentile = 114.72±5.06, mean score fT4<10th percentile = 108.72±5.00, $p < 0.01$), perceptual-manipulative (mean score fT4>10th percentile = 56.66±6.58, mean score fT4<10th percentile = 48.97±5.68, $p < 0.001$), and memory (mean score fT4>10th percentile = 56.63±7.24, mean score fT4<10th percentile = 52.22±7.81, $p < 0.05$) being significantly lower. Results were not significant for verbal, numerical, and motor skills scales.

van Mil et al. (2012): 2,621 pregnant women were tested for maternal levels of fT4 and TSH during the first trimester (mean = 13.4 GW) as part of the Generation R study in the Netherlands. Offspring cognitive development was evaluated using the Parent Report of Children's Abilities, where a cognitive delay was defined based on nonverbal cognitive scores in the 15th percentile. Maternal hypothyroxinemia (fT4 < 11.82 pmol/L) was associated with a statistically significant increased risk of cognitive delay (OR = 1.63; 95% CI: 1.06-2.52; $p = 0.03$). Fetal and infant head sizes were also examined as part of this study.

Wang et al. (2016): Seven prospective cohort studies (summarized individually as Group 1 or Group 2 studies) with a total of 8,273 mother-child pairs were included in a meta-analysis to evaluate the relationship between maternal T4 levels during pregnancy and cognitive development in children. Low maternal T4 levels correlated with a three-fold risk of delayed cognitive development in children when using a random-effect model (random relative risk = 3.08, 95% CI: 1.83, 5.18; $p < 0.001$).

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Appendix F – Bayley Scales of Infant Development

This overview discusses using the BSID as an endpoint to evaluate when considering potential adverse neurodevelopmental impacts in infants or young children.

The BSID is one of the most common tests used to assess neurodevelopment in infants and children. Designed for use in infancy and early childhood, it aims to identify areas of relative impairment or delay and to assist in intervention planning (Florida Partnership for School Readiness, 2004). The BSID was originally published in 1969 and is currently on its third edition (Johnson & Marlow, 2006; van der Meulen & Smrkovsky, 1984). The BSID has long been considered the gold standard for neurodevelopmental assessment of children and has thus been extensively used in neurodevelopmental research (Florida Partnership for School Readiness, 2004). It has also been the primary diagnostic tool for determining eligibility for early intervention services, which are mandated by law in the United States (Gauthier, Bauer, Messinger, & Closius, 1999). It has been commonly used to assess developmental outcomes associated with medical diagnoses such as prematurity, drug exposures, and genetic disorders (Lowe, Erickson, Schrader, & Duncan, 2012).

The first and second editions of the BSID are very similar (Pop et al., 1999, 2003, used Bayley Scale I). Both the first and second editions of the BSID last up to an hour and are usually administered by a trained professional (Johnson & Marlow, 2006; van der Meulen & Smrkovsky, 1984). The revised second edition retained a great amount of the original content, but aimed to extend the maximum testing age from 30 to 42 months, to update content, and to improve the content coverage (Gagnon & Nagle, 2000).

These editions contain two main indices for assessing neurodevelopment in infants and children: the Mental Development Index and the Psychomotor Development Index (Johnson & Marlow, 2006; van der Meulen & Smrkovsky, 1984). The MDI assesses cognitive and language development, while the PDI assesses fine and gross motor skills (Florida Partnership for School Readiness, 2004). Specifically, the MDI contains items related to sensory perception, knowledge, memory, problem solving, and early language (Gauthier et al., 1999). The first and second editions of the BSID additionally contain a scale for evaluating a child's behavior during the assessment; while this scale could be useful in interpreting individual results, it is not typically used in neurodevelopmental research (Johnson & Marlow, 2006; van der Meulen & Smrkovsky, 1984). As is the case for IQ tests, scores on the MDI and PDI are standardized with a mean of 100 and an SD of 15 (Johnson & Marlow, 2006). Scores within 1 SD of the mean are considered to be in the normal range, while scores of 1-2 SD (70-85 points) and more than 2 SD below the mean (under 70 points) are indicative of mild impairment and moderate to severe impairment, respectively (Johnson & Marlow, 2006).

The first edition of the BSID was translated into Dutch and standardized for children in the Netherlands in a 1984 publication by van der Meulen & Smrkovsky. In this version, which was used by Pop et al. (1999, 2003), the mean scores on the MDI and PDI are also 100, with a slightly different SD of 16 (Pop et al., 2003). The Dutch version of the BSID is as faithful a translation as possible and uses the same cut points for impairment as discussed above (Pop et al., 2003; van der Meulen & Smrkovsky, 1984). However, while the Dutch version is a translation of the BSID, Dutch norms may differ from U.S. norms and one study found that "for all subtests… these differences are clinically relevant" (Steenis, Verhoeven, Hessen, & van Baar, 2015).

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The third and most recent edition of the BSID was published in 2006. Intended to provide a more comprehensive assessment of children's neurodevelopment, it eliminates use of the MDI and PDI and replaces them with five scales: cognition, language, motor skills, social-emotional, and adaptive behavior (Johnson & Marlow, 2006). Since the third edition of the BSID is a significant revision and has not been extensively used in research on the association between alterations in thyroid hormone levels and children's neurodevelopment, EPA considers only the first and second editions when referring to the BSID in the remainder of this section.

The BSID has been shown to be a "reliable indicator of the current development and cognitive functioning of the infant" (U.S. EPA, 2013, p. 4-77). Items included on the BSID differ according to the age of the child at the time of administration. For the youngest children (ages 2-4 months), items on the BSID relate to the ability to focus on, track, reach for, and hold simple objects such as cubes (Moore, Goodwin, & Oates, 2008). By ages 9-12 months, items on the BSID assess the ability to perform tasks such as building towers and closing a round container (Moore et al., 2008). For children in the upper end of the age range for the BSID (i.e., around 3 years old), the test includes items that assess picture recognition and visual discrimination skills (Parveen et al., 2014). Items on the BSID for older children are similar to those found on IQ tests (Florida Partnership for School Readiness, 2004). However, the BSID is not intended for use as a measure of intelligence and is thus not necessarily predictive of intellectual ability in later childhood, particularly when administered during the first year of life (McCall, 1989; Niccols & Latchman, 2002).

When considering children who are not at risk and who have normal development, the BSID scores in infancy tend not to be reliable predictors of later cognitive ability in infants. However, the BSID is considered a good predictor of later intelligence for at-risk infants and those with developmental delays (Niccols & Latchman, 2002). In addition, while a very low score (i.e., below 70) on the BSID-II may not necessarily be indicative of severe impairment in later childhood, studies have shown that children with these low scores are at greater risk for impairment and reduced achievement (Johnson & Marlow, 2006). McGrath, Wypij, Rappaport, Newburger, & Bellinger (2004) found that children who scored ≤ 84 on the MDI (i.e., 1 or more SD below the mean) at age 1 year were 2-3 times more likely to have a full-scale IQ score 1 or more SDs below the mean at age 8 than children with scores > 84. The authors concluded that "targeting children with low [BSID] scores at 1 year for intervention services will capture a substantial subgroup of the children at increased risk of cognitive problems at that age" (McGrath et al., 2004). The BSID has high levels of test-retest and inter-rater reliability, with coefficients of approximately 0.8-0.9 (Florida Partnership for School Readiness, 2004).

The above discussion concentrates on the clinical significance of performance on the BSID at the individual level. When considering information to inform the derivation of an MCLG it is necessary to view the adverse health outcome at a population level, to ensure the protection of public health. It could be argued that small changes in the performance by an individual on the BSID is not significant given that they will likely not result in interventions or shifting an individual from a normal score to one that is considered impaired. However, when considering the problem from a population perspective it is necessary to consider how the entire distribution of BSID scores may shift due to alterations in thyroid hormone levels. If the BSID distribution is shifting downward, there will be a significant increase in the proportion of individuals falling into the categories of mild, moderate, or severe impairment. This could in turn result in a significant increase in the number of children who may be at risk for cognitive impairment later in life.

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In conclusion, the BSID is a reliable and valid indicator of neurodevelopment in infancy and early childhood. Additionally, considering information to inform the derivation of an MCLG based on this indicator one should consider the distribution of BSID scores at the population level to understand the public health implications of small shifts at the individual level.

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Appendix G – Studies Examining Associations of Thyroid Hormone/Hypothyroxinemia and Developmental Outcomes

Table G-9. Studies Examining Associations of Thyroid Hormone/Hypothyroxinemia and IQ

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	IQ Age	Effect Estimate for fT4/hX and IQ[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Chevrier et al. (2011) [1] *Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age*	287 mother-child pairs (88% Mexican) from Salinas Valley, CA **Summary**. Results of the analysis did not find a significant relationship between maternal thyroid hormone levels during the second trimester of pregnancy and performance on the Bayley Scale or IQ tests.	fT4 < 6.4	5 yr	-4.12 (-13.73, 5.49)[b] [fT4 measured in ng/dL]
Fan and Wu (2016) [2] *The Impact of Thyroid Abnormalities during Pregnancy on Subsequent Neuropsychological Development of the Offspring: A Meta-Analysis*	4,449 mother-child pairs of various nationalities identified through multiple studies (n_{cases}=310). **Summary**. Children born to hypothyroxinemic mothers had mean intelligence and motor scores 5.7 and 4.2 points lower than non-hypothyroxinemic mothers, respectively.	Multiple studies evaluated, no set definition		*Differences in Mean Score* **-5.69 (-7.98, -3.40) points lower IQ in hX group compared to controls (i.e., non-hypothyroid, defined on study by study basis).**
Ghassabian et al. (2014) [1] *Downstream Effects of Maternal Hypothyroxinemia in Early Pregnancy: Nonverbal IQ and Brain Morphology in School-Age Children*	3,727 Dutch mother-child pairs (n_{cases}=129) **Summary**. Maternal hypothyroxinemia during early pregnancy (mean GW = 13.5) was associated with an average reduction of 4.3 points (p = 0.001, 95% CI: -6.68, -1.81) in children's nonverbal IQ at age 6. Continuous measures of maternal thyroid function (TSH, fT4) across the entire range (not the hypothyroxinemic range) and subclinical hypothyroidism were not significantly associated with nonverbal IQ in 6-year-old children.	fT4 < 5th percentile (< 10.99)	6 yr	-0.24 (0.61, 0.14)[c] [fT4 per SD] **4.32 (-6.68, -1.81)[b] points lower IQ in offspring of maternal hX group compared to offspring of mothers with normal thyroid status (>10.99 pmol/)**

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	IQ Age	Effect Estimate for fT4/hX and IQ[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Grau et al. (2015) [2] *Normal Intellectual Development in Children Born from Women with Hypothyroxinemia During Their Pregnancy*	289 Spanish mother-child pairs at 6-8 years neurocognitive testing (1st trimester cases = 33; 2nd trimester cases = 28) **Summary**. Children of mothers with hypothyroxinemia in the first and second trimester from an iodine-sufficient area did not have adverse neurodevelopmental outcomes (age 6 to 8 with the Wechsler Intelligence Scale for Children) associated with levels of fT4.	fT4 < 10th percentile (< 13.7) (first trimester) fT4 < 10th percentile (<11.5 pmol/L) (second trimester)	6-8 yr	*Comparisons made to individuals with fT4>10th percentile, UIC >150 µg/L; all results are differences in means between groups* First Trimester 0.1 (CI: NR) points lower Verbal comprehension in hX group 3.7 (CI: NR) points higher perceptual reasoning in hX group 0.6 (CI: NR) points higher working memory in hX group 2.7 (CI: NR) points higher total IQ in hX group Second Trimester 1.2 (CI:NR) points lower verbal comprehension in hX group 1.2 (CI:NR) points higher perceptual reasoning in hX group 3.3 points lower working memory in the hX group 2.2 points higher processing speed in the hX group 0.3 points lower total IQ in the hX group

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	IQ Age	Effect Estimate for fT4/hX and IQ[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Korevaar et al. (2016) [1] *Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study*	3,839 Dutch mother-child pairs **Summary.** The authors concluded that both low and high maternal fT4 concentrations during pregnancy were associated with statistically significant lower child IQ and lower gray matter and cortex volume.	N/A	6 yr	*[fT4 natural log transformed]* **Variable** / **β (SE)[d]**: **fT4** — **33.81 (12.25)**; **fT4²** — **-6.235 (2.210)** *Difference in Mean Scores* **Low maternal fT4 associated with 1.5-3.8 point reduction in mean child IQ (range of cutoff levels: <3rd to < 11th) compared to maternal fT4 between 10th - 90th percentile , all p< 0.05[d]**
Moleti et al. (2016) [1] *Effects of Maternal Iodine Nutrition and Thyroid Status on Cognitive Development in Offspring: A Pilot Study*	59 Sicilian mother-child pairs **Summary**. The authors found that maternal iodine status is predictive of neurodevelopmental outcomes in offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and FSIQ, but failed to reach statistical significance.	None reported	6-12 yr	fT4 measured ≤ 12 GW[e] 1.192 (0.980, 1.450) [exp β Verbal IQ] 1.053 (0.881, 1.259) [exp β Performance IQ]] 1.103 (0.928, 1.311) [exp β Full Scale IQ] fT4 measured 13-18 GW[e] 1.217 (1.015 -1.459) [exp β Verbal IQ]

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	IQ Age	Effect Estimate for fT4/hX and IQ[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				1.010 (0.855 -1.194) [exp β Performance IQ]] 1.165 (0.980-1.385) [exp β Full Scale IQ] fT4 measured 19-24 weeks[e] 1.234 (0.991-1.537) [exp β Verbal IQ] 1.125 (0.897-1.411) [exp β Performance IQ] 1.155 (0.937-1.425) [exp β Full Scale IQ] fT4 measured 25-30 weeks[e] 1.137 (0.928-1.393) [exp β Verbal IQ] 1.003 (0.810-1.243) [exp β Performance IQ] 1.031 (0.847-1.254) [exp β Full Scale IQ] fT4 measured GW 31-term[e] 1.191 (0.982-1.445) [exp β Verbal IQ] 1.010 (0.834-1.224) [exp β Performance IQ] 1.070 (0.895-1.280) [exp β Full Scale IQ]

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	IQ Age	Effect Estimate for fT4/hX and IQ[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Vermiglio et al. (2004) [1] *Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild–Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries*	27 Italian mother-child pairs (16 iodine-deficient and 11 iodine-sufficient) **Summary**. There was a quantifiable relationship between fT4 at GW 20 and IQ at 8 to 10 years of age. Authors did not present the equation representing the relationship but did present r = 0.56, p <0.005 for the regression. Using the linear regression function in Excel on the extracted data, it was determined that for every 1 pmol/L change in fT4 there is an estimated 2.6 point change in IQ.	fT4 < 11.0	8-10 yr	**2.6 (0.90, 4.33)[f]**

CI = confidence interval; GW = gestational weeks; hX = hypothyroxinemia; NR = not reported

[a] fT4 measured in pmol/L unless otherwise noted

[b] Model adjusted for maternal age; income; employment status at 6 months; country of birth; Diet Quality Index; delivery complications; Peabody Picture and Vocabulary Test (PPVT) score; child 5-minute Apgar score, hospitalization at 1 year; number of children in home at 1 and 2 years, home density at 2 years, family structure at 1 year; and season of assessment.

[c] Model adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.

[d] Analysis were adjusted for gestational age at blood sampling, maternal age, smoking, BMI, parity, education level, ethnicity, fetal sex and birth weight

[e] Model adjusted for maternal age; gestational age at birth; birthweight; child age at time of IQ test; maternal fT4, fT4, and TSH various times during gestation; maternal urinary iodide excretion; family socioeconomic status; maternal parity; sex of child; breastfeeding; major maternal stressful life-events; and maternal/parental education.

[f] Based on digitization of figures representing regression analysis presented in the paper. The study author presented results using fT4 units of ng/dL. EPA converted to pmol/L using a conversion factor of 12.87 (CTDS Laboratories) for comparison to BBDR output.

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Table G-10. Studies Examining Associations of Thyroid Hormone/Hypothyroxinemia and Bayley MDI

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	MDI Age	Effect Estimate for fT4/hX and MDI[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted)] Underlined & Bold indicate statistically significant at p < 0.05
Chevrier et al. (2011) [1] *Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age*	287 mother-child pairs (88% Mexican) Salinas Valley, CA **Summary**. Results of the analysis did not find a significant relationship between maternal thyroid hormone levels during the second trimester of pregnancy and performance on the Bayley Scale or IQ tests.	fT4 < 6.4	6 mo 1 yr 2 yr	[fT4 measured in ng/dL] -3.14 (-7.65, 1.36)[b] -0.48 (-6.22, 5.26)[c] -4.29 (-11.60, 3.02)[d]
Costeira et al. 2011 [2] *Psychomotor Development of Children from an Iodine-Deficient Region*	86 Portuguese mother-child pairs from iodine-deficient region (n_{cases} = 8) **Summary**. Children born to mothers with low fT4 had increased odds of mild-to-severe delay in psychomotor development compared to children born to mothers with fT4 within the population reference range. Neonatal thyroid status did not influence development.	fT4 < 10th percentile (<9.0 pg/ml or < 11.6 pmol/L)	12 mo 24 mo	*Difference in mean score*[e] 8.9 (CI: NR) points lower MDI in offspring of mothers in hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile, fT4 measured in the 3rd trimester 10.8 (CI: NR) points lower MDI in offspring of mothers in hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile, fT4 measured in the 1st trimester

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	MDI Age	Effect Estimate for fT4/hX and MDI[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted)] Underlined & Bold indicate statistically significant at p < 0.05
Craig et al. (2012) [2] *Mid-Gestational Maternal Free Thyroxine Concentration and Offspring Neurocognitive Development at Age Two Years*	Mother-child pairs in Maine, matched on fT4 levels (case: 3rd percentile or less n_{cases}=98; control: 10th to 90th percentile fT4 $n_{control}$= 98) **Summary**. Unadjusted scores on the Bayley Scale III were lower at 2 years of age in children born to mothers with low fT4 in the second trimester (17 GW) as compared to children born to mothers with fT4 levels within the population reference range (10th to 90th percentile, or 12.9 to 17.2 pmol/L). After adjustment for confounding variables, differences were diminished, but 10th percentile fT4 levels were still associated with lower scores on the Bayley Scale.	fT4 ≤ 3rd percentile (< 11.8)	2 yr	*Mean matched difference between control and hX group*[f] -1.4 (-4.9, 2.0) points lower MDI in offspring of hX group compared to offspring of mothers with fT4 between the 10th and 90th percentile (n = 98 matched pairs) -1.0 (-5.0, 3.1) points lower MDI in offspring of hX group compared to offspring of mothers with fT4 between the 10th to 49th percentile (n = 59 matched pairs) 0.2 (-6.3, 6.8) points lower MDI in offspring of hX group compared to offspring of mothers with fT4 between the 50th to 90th percentile (n = 39 matched pairs)
Júlvez et al. (2013) [2] *Thyroxine Levels During Pregnancy in Healthy Women and Early Child Neurodevelopment*	1,643 Spanish mother-child pairs (n_{cases} = 164) **Summary**. Children born to mothers with lower fT4 (<10th percentile (<8.89 pmol/L, measured between 8-20 weeks, median 13 weeks gestation)) show a decrease in Bayley's Score compared to children born to mothers with fT4 > 10th percentile.	Low fT4 (less than 10th (8.89), 5th (8.39) or 2.5th (8.10) percentile)	14 mo	**-2.23 (-4.47,- 0.01) [< 10th]**[g] -3.04 (-6.09, 0.01) [< 5th][g] -3.11 (-7.38, 1.17) [< 2.5th][g] **p for trend = 0.03** **-1.26 (-2.37, -0.10) [ordinal]**[g,h]

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	MDI Age	Effect Estimate for fT4/hX and MDI[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted)] Underlined & Bold indicate statistically significant at p < 0.05
Li et al. (2010) [2] *Abnormalities of Maternal Thyroid Function During Pregnancy Affect Neuropsychological Development of Their Children at 25-30 Months*	57 Chinese mother-child pairs (n_{cases} = 19) **Summary**. Children of hypothyroxinemic women had significantly lower mean mental and psychomotor development (Bayley's) scores at 25-30 months compared to children of non-hypothyroxinemic women (fT4 measured between 16 and 20 weeks gestation).	fT4 < 5th percentile (< 11.9)	25-30 mo	**9.3 (CI: NR) points lower MDI in hX group compared to controls (i.e., non-hX mothers defined based on tT4 less than the 2.5th percentile)**
Pop et al. (1999) [1] *Low Maternal Free Thyroxine Concentrations During Early Pregnancy Are Associated with Impaired Psychomotor Development in Infancy*	220 children of Dutch women from iodine-sufficient area, 22 with fT4 < 10th percentile **Summary**. Children of mothers with fT4 concentration in the lowest fT4 5th and 10th percentiles had lower scores on the Mental Development Index subscale, although these differences were not significant.	< 10th percentile (< 10.4)	10 mo	*Difference in Mean Score* Not reported in the paper because did not find statistically significant difference

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	MDI Age	Effect Estimate for fT4/hX and MDI[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted)] Underlined & Bold indicate statistically significant at p < 0.05
Pop et al. (2003) [1] *Maternal Hypothyroxinemia during Early Pregnancy and Subsequent Child Development: A 3-Year Follow-Up Study*	Age 1: 63 cases (with maternal hX)and 62 controls (without maternal hX) Age 2: 57 cases (with maternal hX) 58 controls (without maternal hX); Dutch women and their offspring **Summary**. Maternal fT4 levels in the lowest 10th percentile in the first trimester were significantly associated with a clinically relevant difference in psychomotor and mental development among 2-year-olds. Authors did not present the equation representing the relationship but did present $r^2 = 0.13$, p =0.006 for the regression. Using the linear regression function in Excel on the extracted data, it was determined that for every 1 pmol/L change in fT4 there is an estimated 6.3 point change in IQ.	< 10th percentile (i.e., fT4 ≤ 12.4)	2 yr 1 yr 2 yr	**6.3 (1.9, 10.6)**[i] *Difference in Mean Score:* **10 points (4, 16) lower MDI in offspring of mothers in the hX group compared to offspring of mothers with fT4 between the 50th and 90th percentiles** **8 points (4, 12) lower MDI in the offspring of mothers in the hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile**
Velasco et al. 2009 [1] *Effect of Iodine Prophylaxis during Pregnancy on Neurocognitive Development of Children during the First Two Years of Life*	133 Spanish women who took 300 µg/day potassium iodide from the first trimester and 61 controls **Summary**. Among a group of women with sufficient iodine intake through iodine supplementation, fT4 levels in the third trimester correlated significantly with psychomotor development in infants aged 3 to 18 months	None	6 mo	*Difference in Mean Score:* 0.3 (CI: NR) point higher MDI score in offspring of the group that took supplements of 300 µg/day compared offspring of mothers in the control group.

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	MDI Age	Effect Estimate for fT4/hX and MDI[a] [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted)] Underlined & Bold indicate statistically significant at p < 0.05

CI = confidence interval; GW = gestational weeks; hX = hypothyroxinemia; NR = not reported

[a] fT4 measured in pmol/L unless otherwise noted

[b] Model adjusted for maternal age, employment status at enrollment and at the 6-month visit, country of birth, time lived in the US, Diet Quality Index, blood lead levels and delivery complications, child hospitalization before 6 months, season of assessment and psychometrician.

[c] Model adjusted for maternal age, employment status at enrollment and at the 6-month visit, country of birth, time lived in the US, Diet Quality Index, Kotelchuck Adequacy of Prenatal Care Utilization Index, blood lead levels and delivery complications, PPVT score, child age, preterm birth, child hospitalization before 6 months and 1 year, family structure at 1 year, season, and language spoken at the time of assessment.

[d] Model adjusted for maternal age, income, employment status at enrollment and at the 6-month and 1 year visits, country of birth, US, Diet Quality Index, Kotelchuck Adequacy of Prenatal Care Utilization Index, blood lead levels and delivery complications, PPVT score, child hospitalization at 1 year, number of children in the home at 6 months, home density at 2 years, family structure at 1 year, season, psychometrician and language of assessment.

[e] Model adjusted for maternal age, parity, socioeconomic-cultural status, length of breastfeeding, use of alcohol and tobacco during pregnancy, children's sex, gestational age, type of delivery, Apgar score, birthweight, body length, and head circumference.

[f] Adjusted for gestational age, child's age at testing, maternal weight, and years of education

[g] Models were adjusted for region, sex, psychologist, gestational age and weight at birth, circulating vitamin D during pregnancy and year-season of sampling, urine cotinine levels during pregnancy, TSH, maternal education and parental social class, maternal parity, father's age at birth, quality of the test and child neurologic pathology

[h] Free T4 concentrations (standardized by gestational age at sampling) were dichotomized using the percentiles (PC) 90th, 95th, and 97.5th, and 10th, 5th, and 2.5th, respectively, as cut points. Reference categories were defined by those children whose mother had TSH or free T4 levels below and above the cut points, respectively. Ordinal variables were formed with all the percentile categories merged into a unique variable

[i] Based on digitization of figures representing regression analysis presented in the paper.

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Table G-11. Studies Examining Associations of Thyroid Hormone/Hypothyroxinemia and Psychomotor Development (PDI)

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	PDI Age	Effect Estimate for fT4/hX and PDI [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Chevrier et al. (2011) [1] *Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age*	287 mother-child pairs (88% Mexican) from Salinas Valley, CA **Summary**. Results of the analysis did not find a significant relationship between maternal thyroid hormone levels during the second trimester of pregnancy and performance on the Bayley Scale or IQ tests.	fT4 < 6.4		[fT4 measured in ng/dL)
			6 mo	-3.27 (-9.36, 2.82)[a]
			1 yr	-6.40 (-13.89, 1.08)[b]
			2 yr	-2.67 (-8.95, 3.62)[c]
Costeira et al. 2011 [2] *Psychomotor Development of Children from an Iodine-Deficient Region*	86 Portuguese mother-child pairs from iodine-deficient region (n_{cases} = 8) **Summary**. Children born to mothers with low fT4 had increased odds of mild-to-severe delay in psychomotor development compared to children born to mothers with fT4 within the population reference range. Neonatal thyroid status did not influence development.	fT4 < 10th percentile (< 11.6)		*Difference in Mean Score:*
			18 mo	**-12.8 (CI: NR) points lower PDI score in offspring of mothers in the hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile, fT4 measured in the 1st trimester**
			24 mo	**-13.6 (CI: NR) points lower PDI score in in offspring of mothers in the hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile, fT4 measured in the 1st trimester**

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	PDI Age	Effect Estimate for fT4/hX and PDI [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Craig et al. (2012) [2] *Mid-Gestational Maternal Free Thyroxine Concentration and Offspring Neurocognitive Development at Age Two Years*	Mother-child pairs in Maine, matched on fT4 levels (case: 3rd percentile or less n_{cases}=98; control: 10th to 90th percentile fT4 $n_{control}$= 98) **Summary**. Unadjusted scores on the Bayley Scale III were lower at 2 years of age in children born to mothers with low fT4 in the second trimester (17 GW) as compared to children born to mothers with fT4 levels within the population reference range (10th to 90th percentile, or 12.9 to 17.2 pmol/L). After adjustment for confounding variables, differences were diminished, but 10th percentile fT4 levels were still associated with lower scores on the Bayley Scale.	fT4 ≤ 3rd percentile (< 11.8)	2 yr	*Difference in Mean Score* -1.9 (-6.1, 2.4) points lower PDI score in hX group compared to offspring of mothers with fT4 between the 10th and 90th percentile (n = 98 matched pairs) -2.1 (-7.3, 3.1) points lower PDI score in hX group compared to offspring of mothers with fT4 between the 10th and 49th percentile (n = 59 matched pairs) -1.1 (-9.2, 7.1) points lower PDI score in hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile (n= 39 matched pairs)
Júlvez et al. (2013) [2] *Thyroxine Levels During Pregnancy in Healthy Women and Early Child Neurodevelopment*	1,643 Spanish mother-child pairs (n_{cases} = 164) **Summary**. Children born to mothers with lower fT4 (<10th percentile (<8.89 pmol/L)) show a decrease in Bayley's Score compared to children born to mothers with fT4 > 10th percentile.	Low fT4 (less than 10th (8.89), 5th (8.39) or 2.5th (8.10) percentile)	14 mo	0.28 (-1.94, 2.51) [< 10th] [d] -1.17 (-4.20, 1.86) [< 5th] [d] -1.10 (-5.36, 3.15) [< 2.5th] [d] p for trend = 0.77 -0.17 (-1.31, 0.97) points lower in PDI score in hX group [ordinal] [e]

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	PDI Age	Effect Estimate for fT4/hX and PDI [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Li et al. (2010) [2] *Abnormalities of Maternal Thyroid Function During Pregnancy Affect Neuropsychological Development of Their Children at 25-30 Months*	57 Chinese mother-child pairs (n_{cases} = 19) **Summary**. Children of hypothyroxinemic women had significantly lower mean mental and psychomotor development (Bayley's) scores at 25-30 months compared to children of non-hypothyroxinemic women.	fT4 < 5th percentile (< 11.9)	25-30 mo	**-7.6 (CI: NR) point lower PDI score in hX group compared to controls (i.e., non-hX mothers defined on a study by study basis)**
Pop et al. (1999) [1] *Low Maternal Free Thyroxine Concentrations During Early Pregnancy Are Associated with Impaired Psychomotor Development in Infancy*	220 children of Dutch women from iodine-sufficient area, 22 with fT4 < 10th percentile **Summary**. Maternal fT4 levels in the lowest 10th percentile in the first trimester among an iodine-sufficient population were significantly associated with reduced psychomotor development in 10-month-old infants. Authors did not present the equation representing the relationship but did present r^2 = 0.46, p =0.03 for the regression. Using the linear regression function in Excel on the extracted data, it was determined that for every 1 pmol/L change in fT4 there is an estimated 8.5 point change in PDI.	< 10th percentile (< 10.4)	10 mo	**8.5 (0.01, 17.0)**[f] [only for women with fT4< 10th percentile] *Difference in Mean Score:* **[5th percentile] 14.1 (5.9, 22.3) point lower PDI score difference in hX group compared to > 5th percentile** **[10th percentile] 7.4 (1.1, 13.9) point lower PDI score difference in hX group compared to > 10th percentile** Significant difference in PDI score not seen when comparing maternal fT4 at the 15th percentile, or greater, to the rest of the group.

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	PDI Age	Effect Estimate for fT4/hX and PDI [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Pop et al. (2003) [1] *Maternal Hypothyroxinemia during Early Pregnancy and Subsequent Child Development: A 3-Year Follow-Up Study*	Age 1: 63 cases (with maternal hX) and 62 controls (without maternal hX) Age 2: 57 cases (with maternal hX) 58 controls (without maternal hX); Dutch women and their offspring **Summary**. Maternal fT4 levels in the lowest 10th percentile in the first trimester were significantly associated with a clinically relevant difference in psychomotor and mental development among 2-year-olds. Authors did not present the equation representing the relationship but did present $r^2 = 0.13$, p =0.006 for MDI and $r^2 = 0.23$, P = 0.001 for PDI. Using the linear regression function in Excel on the extracted data, it was determined that for every 1 pmol/L change in fT4 there is an estimated 8.4 point change in PDI and 6.3 point change in MDI.	< 10th percentile (i.e., fT4 ≤ 12.4)	2 yr	**8.4 (4.0, 12.8)**[f] [only for women with fT4< 10th percentile]
			1 year	*Difference in Mean Score* **8 (3, 12) point lower PDI score in hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile**
			2 year	**10 (6, 16) point lower PDI score in hX group compared to offspring of mothers with fT4 between the 50th and 90th percentile**
Velasco et al. 2009 [1] *Effect of Iodine Prophylaxis during Pregnancy on Neurocognitive Development of Children during the First Two Years of Life*	133 Spanish women who took 300 µg/day potassium iodide from the first trimester and 61 controls. **Summary**. Among a group of women with sufficient iodine intake through iodine supplementation, fT4 levels in the third trimester correlated significantly with psychomotor development in infants aged 3 to 18 months.	None	6 mo	**5.1 (2.1, 8.2)**[f] *Difference in Mean Score* **6.09 point higher PDI score in offspring of mothers in 300 µg/day supplement group compared to control group**

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	PDI Age	Effect Estimate for fT4/hX and PDI [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05

CI = confidence interval; GW = gestational weeks; hX = hypothyroxinemia; NR = not reported

[a] Model adjusted for maternal age, employment status at enrollment and at the 6-month visit, country of birth, time lived in the US, Diet Quality Index, blood lead levels and delivery complications, child hospitalization before 6 months, season of assessment and psychometrician.

[b] Model adjusted for maternal age, employment status at enrollment and at the 6-month visit, country of birth, time lived in the US, Diet Quality Index, Kotelchuck Adequacy of Prenatal Care Utilization Index, blood lead levels and delivery complications, PPVT score, child age, preterm birth, child hospitalization before 6 months and 1 year, family structure at 1 year, season, and language spoken at the time of assessment.

[c] Model adjusted for maternal age, income, employment status at enrollment and at the 6-month and 1 year visits, country of birth, US, Diet Quality Index, Kotelchuck Adequacy of Prenatal Care Utilization Index, blood lead levels and delivery complications, PPVT score, child hospitalization at 1 year, number of children in the home at 6 months, home density at 2 years, family structure at 1 year, season, psychometrician and language of assessment.

[d] Models were adjusted for region, sex, psychologist, gestational age and weight at birth, circulating vitamin D during pregnancy and year-season of sampling, urine cotinine levels during pregnancy, TSH, maternal education and parental social class, maternal parity, father's age at birth, quality of the test and child neurologic pathology

[e] Free T4 concentrations (standardized by gestational age at sampling) were dichotomized using the percentiles (PC) 90th, 95th, and 97.5th, and 10th, 5th, and 2.5th, respectively, as cut points. Reference categories were defined by those children whose mother

[f] Based on digitization of figures representing regression analysis presented in the paper.

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Table G-12. Studies Examining Associations of Thyroid Hormone/Hypothyroxinemia and Various Developmental Outcomes

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Berbel et al. (2009) [2] *Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation*	Spanish mother-child pairs in 3 groups **Group 1:** fT4> 20th percentile at 4-6 gestational weeks and term, supplemented with 200 µg/day potassium iodine through term and lactation. Neurocognitive evaluation was done on children with mothers fT4>20th percentile at 4-6 weeks and at term. (n=13) **Group 2:** mildly hypothyroxinemic at 12-14 gestational weeks, supplemented with 200 µg/day potassium iodine through term and lactation. Neurocognitive evaluation done on children with maternal fT4 <10th percentile at 12-14 weeks and fT4>20th percentile at term (n=12) **Group 3:** enrolled at full term at which time they were supplemented with 200 µg/day potassium iodine throughout lactation. Neurocognitive evaluations done on children born to mother that had fT4<10th percentile at term. (n=19) **Summary**. A delay of 6–10 weeks in iodine supplementation of hypothyroxinemic mothers at the beginning of gestation increased the risk of neurodevelopmental delay.	fT4 < 10th percentile (< 10.6)	18 mo	Brunet-Lézine Development Quotients	*Difference in Mean Scores* **14.3 (CI: NR) points lower development quotient scored in Group 3 compared to Group 1.** **9.6 (CI: NR) points lower development quotient score in Group 2 compared to Group 1.** Difference between Group 2 and Group 3 in regard to development quotient scores was not statistically significant and not presented in the article.
				Accelerated performance	In Group 1 15.4% of children showed accelerated performance vs. 8.3% in Group 2.
				Normal performance	Normal performance increased in Group 1 (84.6%) compared to Group 2 (25% and Group 3 (36.8%)
				Delayed performance	Delayed performance only observed in Group 2 (25%)

ED_005043_00079785-00052

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
					and Group 3 (36.8%)
				Fine and gross motor coordination and socialization scales	**Difference in fine, gross motor, and socialization scales were statistically significantly different with group 1 having the highest quotients (scores not reported).** Language quotients did not differ between groups.
Chevrier et al. (2011) [1] *Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age*	287 mother-child pairs (88% Mexican) from Salinas Valley, CA **Summary**. Results of the analysis did not find a significant relationship between maternal thyroid hormone levels during the second trimester of pregnancy and performance on the Bayley Scale or IQ tests.	fT4 < 6.4	5 yr[a]	*Motor Development* WRAVMA Pegboard – Dominant Pegboard – Nondominant McCarthy Draw-a-child Gross Motor – Leg Gross Motor – Arm *Language Development* WPPSI Vocabulary PPVT *Memory* McCarthy Words and Sentences Digit Span Forward Digit Span Backward *School Readiness* Woodcock-	[fT4 measured in ng/dL][b] -3.76 (-15.45, 7.93) -4.21 (-16.03, 7.61) -5.98 (-16.74, 4.77) -0.14 (-1.60, 1.32) 0.08 (-1.51, 1.66) 0.21 (-1.98, 1.57) -2.71 (-14.18, 8.77) 0.10 (-11.32, 11.52) 4.06 (-4.72, 12.83) 4.43 (-2.55, 11.42)

ED_005043_00079785-00053

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Johnson/Muñoz	
				Letter-Word	-1.86 (-9.33, 5.60)
				Applied Problems	-3.82 (-14.06, 6.42)
				Attention	
				CBCL	
				ADHD	-0.10 (-2.03, 1.82)
				KCPT	
				ADHD Conf. Index	7.52 (-4.86, 19.91)
Finken et al. (2013) [1]	1,765 Dutch mother-child pairs (n_{cases} = 175) **Summary**. Continuous maternal fT4 levels at a median of 12.9 weeks were inversely associated with the reaction time variability among 5- to 6-year-old children (an increase in the reaction time SD of 4.9 ms was associated with every 1 pmol/L reduction in maternal fT4). Considering fT4 as a categorical variable demonstrated that there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time, when comparing the offspring of hypothyroxinemic to non-hypothyroxinemic mothers.	fT4 < 10th percentile (< 7.7)	5-6 yr		all hX comparisons [hX] are made comparing to children born to hX mothers to children whose mothers had fT4> 10th percentile
				Baseline[c]	
				Mean reaction time, ms	-4.5 (-9.0, 0.1) [fT4][d] **39.5 (17.6, 61.4) [hX][d]**
				Reaction time, SD, ms	**-4.9 (-9.5, -0.2) [fT4]** **41.2 (18.7, 63.7) [hX]**
				Pursuit	
				Deviation, mm	-0.01 (-0.22, 0.21) [fT4] -0.20 (-1.24, 0.83) [hX]
				SD of deviation, mm	0 (-0.20, 0.21) [fT4] -0.29 (-1.29, 0.70) [hX]
				Tracking	
				Mean distance, mm	-0.01 (-0.11, 0.09) [fT4] -0.18 (-0.67, 0.31) [hX]

ED_005043_00079785-00054

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Accuracy stability, mm	0.04 (-0.06, 0.15) [fT4] -0.14 (-0.65, 0.38) [hX]
				Movement speed, s	-0.08 (-0.34, 0.18) [fT4] -0.09 (-1.35, 1.18) [hX]
				Response Organization Objects	
				Part 1 (compatible) Mean reaction time, ms	-5.1 (-12.1, 1.8) [fT4] -0.1 (-34.5, 34.3) [hX]
				Reaction time, SD, ms	-1.7 (-7.4, 3.9) [fT4] 0.3 (-27.7, 28.3) [hX]
				Part 2 (incompatible) Mean reaction time, ms	2.0 (-7.6, 11.6) [fT4] 9.6 (-37.7, 57.0) [hX]
				Reaction time, SD, ms	0.9 (-6.7, 8.6) [fT4] -14.8 (-52.2, 22.5) [hX]
Ghassabian, Henrichs, and Tiemeier (2014) [2] *Impact of Mild Thyroid Hormone Deficiency in Pregnancy on Cognitive Function in Children: Lessons from the Generation R Study*	3,903 Dutch mother-child pairs the novel analysis (n_{cases} = 129) **Summary**. This paper reviews the literature from the Generation R cohort and presents novel results related to ADHD and maternal hypothyroxinemia. In summary, prenatal exposure to maternal hypothyroxinemia increased the risk of ADHD, expressive language delay, and nonverbal cognitive delay in preschool-age children.	Severe: < 5th percentile	1.5 yr and 2.5 yr	Attention deficit/hyperactivity problems	0.12 (-0.04, 0.27) [hX][e]
Grau et al. (2015) [2} *Normal Intellectual*	455 Spanish mother-child pairs at age 1 (1 yr 1st trimester cases = 47; 1 yr 2nd	fT4 < 10th percentile (< 13.7)	1 yr	Brunet-Lézine scale	*Comparisons made to individuals with fT4>10th percentile, UIC >150 µg/L; all*

ED_005043_00079785-00055

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Development in Children Born from Women with Hypothyroxinemia During Their Pregnancy	trimester cases = 42) Summary. Children of mothers with hypothyroxinemia in the first and second trimester from an iodine-sufficient area did not have adverse neurodevelopmental outcomes (assessed at age 1 with the Brunet-Lezine scale) associated with levels of fT4.				*results are differences in means between groups* fT4 measured in first trimester 1.2 (CI: NR) points lower postural control in hX group 1.9 (CI: NR) points lower coordination/oculomotor in hX group 0.2 (CI: NR) points higher language/communication in hX group 1.7 (CI: NR) points lower sociability in hX group 1.4 (CI: NR) points lower global mean score in hX group fT4 measured in second trimester 1.1 (CI:NR) points lower postural control in hX group 1.0 (CI:NR) points lower coordination/oculomotor in hX group 0.8 (CI:NR) points higher

ED_005043_00079785-00056

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
					language/communication in the hX group 3.5 (CI:NR) points lower sociability in hX group 1.2 (CI:NR) points lower global mean score in hX group
Gyllenberg et al. (2016) [1] *Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort*	1,010 Finnish mother-child pairs (n_{cases} = 107 hX mothers) **Summary**. An association between fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range) and odds of schizophrenia diagnosis was found using conditional logistic regression. However, this relationship was attenuated after controlling for smoking. Considering fT4 as a categorical variable demonstrated that 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.	fT4 ≤ 10th percentile (≤ 14.03)	0-26 years		*Odds ratio of offspring schizophrenia comparing children born to mothers with hX during pregnancy to children whose mothers did not have hX*
				Unadjusted	**1.75 (1.22, 2.50) [hX]** **0.54 (0.31, 0.94) [log fT4]**
				Individually adjusted for maternal psychiatric history	**1.92 (1.30, 2.83) [hX]** **0.53 (0.30, 0.94) [log fT4]**
				Individually adjusted for province of birth	**1.78 (1.23, 2.57) [hX]** **0.57 (0.33, 0.999) [log fT4]**
				Individually adjusted for maternal smoking during early gestation	**1.62 (1.12, 2.37) [hX]** 0.71 (0.39, 1.27) [log fT4]
				Adjusted for maternal psychiatric history, province of birth, and	**1.70 (1.13, 2.55) [hX]** 0.74 (0.40, 1.38) [log fT4]

ED_005043_00079785-00057

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				maternal smoking	
Henrichs et al. (2010) [1] *Maternal Thyroid Function during Early Pregnancy and Cognitive Functioning in Early Childhood: The Generation R Study*	3,659 Dutch mother-child pairs (n = 3,409 at 18 months for the per SD analysis, 2,736 for the mild and severe hX analysis; n = 2,779 at 30 months and 2,225 at mild and severe hX analysis, n = 3,643 at 18 and 30 months for the per SD analysis and 2,926 for the mild and severe hX analysis) (n = 2,606 for nonverbal cognitive delay per SD of fT4 analysis and 2,086 for mild and severe hX analysis) **Summary**. Severe maternal hypothyroxinemia was associated with expressive language delay at 18 and 30 months and non-cognitive delay at 30 months. Further, there was an increase in the odds of expressive language delay and non-cognitive delay when comparing the offspring of children exposed to mild versus severe maternal hypothyroxinemia, suggesting a potential dose-response between the severity of hypothyroxinemia and expressive language delay and non-cognitive delay. Additionally, maternal fT4 levels per SD were associated with a reduction in odds of expressive language delay at 30 months (OR = 0.84 per SD of fT4).	Mild: fT4 < 10th percentile (< 11.76) Severe: fT4 < 5th percentile (< 10.96)	18 mo 30 mo	Expressive Language Delay	*Odds Ratio (OR)*[f] Age 18 mo 0.95 (0.83, 1.09), fT4 per SD 1.33 (0.91, 1.94) [mild hX] **1.77 (1.10, 2.84) [severe hX]** Age 30 mo **0.84 (0.71, 0.99), fT4 per SD** 1.47 (1.00, 2.17) [mild hX] **1.78 (1.07, 2.94) [severe hX]** Age 18 and 30 mo 0.90 (0.80-1.01), fT4 per SD **1.44 (1.09, 1.91) [mild hX]** **1.80 (1.24, 2.61) [severe hX]**
				Nonverbal cognitive delay	Age 30 mo 0.85 (0.72, 1.01), fT4 per SD 1.37 (0.90, 2.07) [mild hX] **2.03 (1.22, 3.39) [severe hX]**

ED_005043_00079785-00058

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Kooistra, Crawford, van Baar, Brouwers, and Pop (2006) [2] *Neonatal Effects of Maternal Hypothyroxinemia During Early Pregnancy*	204 Dutch mother-child pairs (n_{cases} = 108) **Summary**. Infants of women with hypothyroxinemia at 12 GW had a lower neonatal Behavioral Assessment Scale orientation index compared with infants of non-hypothyroxinemic women. Neonatal thyroid hormone levels were not assessed in regard to neurodevelopment.	fT4 < 10th percentile (< 10.4)	3 weeks	*Neonatal behavioral Assessment Scale (NBAS)*	*Odds Ratio*
				Below 1-SD of orientation cluster (12 wk gestation)	**0.17 (0.05, 0.51)**
				Below 1-SD of orientation cluster (32 wk gestation)	1.02 (0.83, 1.25)
Modesto et al. (2015) [1] *Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children*	3,873 Dutch mother-child pairs (n_{cases} = 127) **Summary**. Maternal hypothyroxinemia in early pregnancy was associated with higher ADHDi scores in 8-year-old children compared with non-exposed children, after adjusting for confounders (7% increase in ADHDi scores (95% CI: 3%-15%)). When considering fT4 as a continuous variable, the association between maternal fT4 and offspring ADHDi scores was attenuated with the adjustment of confounders. Parent-reported oppositional scores of offspring of hX mothers were also evaluated but did not produce statistically significant results compared to non-hX mothers.	fT4 < 5th percentile (< 0.85 ng/dL or 10.94 pmol/L)	8 yr	*Parent Reported ADHDi Score*	[fT4 measured in ng/dL]
				Maternal Hypothyroxinemia	
				Unadjusted	**0.08 (0.01, 0.15)**
				Adjusted for age and sex	**0.08 (0.01, 0.15)**
				Fully adjusted model[g]	**0.07 (0.003, 0.14)**
				fT4 Level per SD	
				Unadjusted	-0.01 (-0.02, 0.01)
				Adjusted for age and sex	-0.01 (-0.02, 0.01)
				Fully adjusted model[g]	-0.01 (-0.02, 0.01)
				Maternal Hypothyroxinemia (TSH cut point 0.03-4.04 mIU/L)	
				Unadjusted	0.05 (-0.01, 0.11)
				Adjusted for age and sex	0.05 (-0.01, 0.11)
				Fully adjusted model[g]	0.05 (-0.01, 0.11)

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ED_005043_00079785-00059

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Maternal Hypothyroxinemia (gestational age < 13 weeks)	
				Unadjusted	**0.17 (0.03, 0.31)**
				Adjusted for age and sex	**0.15 (0.01, 0.28)**
				Fully adjusted model[g]	0.13 (-0.01, 0.26)
				fT4 per SD (gestational age < 13 weeks	
				Unadjusted	**-0.02 (-0.04, -0.004)**
				Adjusted for age and sex	**-0.02 (-0.04, -0.001)**
				Fully adjusted model[g]	-0.02 (-0.03, 0.003)
				Parent-Reported Oppositional Score Maternal Hypothyroxinemia	
				Unadjusted	0.02 (-0.04, 0.08)
				Adjusted for age and sex	0.02 (-0.04, 0.08)
				Fully adjusted model[g]	0.02 (-0.04, 0.08)
				fT4 Level per SD	
				Unadjusted	0 (-0.1, 0.01)
				Adjusted for age and sex	0 (-0.1, 0.01)
				Fully adjusted model[g]	0 (-0.1, 0.01)
Noten et al. (2015) [1] *Maternal Hypothyroxinemia in*	1,196 Dutch mother-child pairs (n_{cases} = 118) **Summary**. Maternal hypothyroxinemia at the end of the first trimester was associated with	fT4 level less than the 10th percentile of distribution (<	5 yr	*Arithmetic Test Poor school performance* fT4, continuous	*Odds Ratio*

ED_005043_00079785-00060

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
Early Pregnancy and School Performance in 5-Year-Old Offspring	reduced arithmetic test performance in 5-year-old offspring. Inverse probability weighting demonstrates that non-response bias may be present in this study, and thus the results should be interpreted with caution.	8.06 pmol/L in their sample)		Unadjusted	0.88 (0.77, 1.02)
				Adjusted[h]	0.92 (0.80, 1.07)
				Hypothyroxinemia	
				Unadjusted	**1.91 (1.15, 3.17)**
				Adjusted[h]	1.54 (0.89, 2.66)
				Arithmetic Test Subnormal school performance	
				fT4, continuous	
				Unadjusted	**0.89 (0.81, 0.98)**
				Adjusted[h]	0.92 (0.83, 1.02)
				Hypothyroxinemia	
				Unadjusted	**1.89 (1.26, 2.82)**
				Adjusted[h]	**1.61 (1.05, 2.47)**
				Language Test Poor school performance	
				fT4, continuous	
				Unadjusted	0.95 (0.84, 1.08)
				Adjusted[h]	1.02 (0.90, 1.16)
				Hypothyroxinemia	
				Unadjusted	**1.72 (1.05, 2.82)**
				Adjusted[h]	1.23 (0.71, 2.13)
				Language Test Subnormal school performance	
				fT4, continuous	
				Unadjusted	0.98 (0.90, 1.08)
				Adjusted[h]	1.36 (0.91, 2.07)

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ED_005043_00079785-00061

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Hypothyroxinemia	
				Unadjusted	1.36 (0.91, 2.07)
				Adjusted[h]	1.09 (0.70, 1.70)
				Arithmetic Test Poor school performance	*Inverse Probability Weighted Analyses*
				fT4, continuous	
				Unadjusted	0.92 (0.77, 1.10)
				Adjusted[h]	0.95 (0.81, 1.12)
				Hypothyroxinemia	
				Unadjusted	**1.83 (1.09, 3.09)**
				Adjusted[h]	1.44 (0.81, 2.57)
				Arithmetic Test Subnormal school performance	
				fT4, continuous	
				Unadjusted	0.93 (0.83, 1.04)
				Adjusted[h]	0.95 (0.86, 1.06)
				Hypothyroxinemia	
				Unadjusted	**1.76 (1.16, 2.67)**
				Adjusted[h]	1.48 (0.94, 2.32)
				Language Test Poor school performance	
				fT4, continuous	
				Unadjusted	0.99 (0.86, 1.15)
				Adjusted[h]	1.05 (0.92, 1.19)
				Hypothyroxinemia	
				Unadjusted	**1.66 (0.99, 2.75)**

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ED_005043_00079785-00062

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Adjusted[h]	1.20 (0.70, 2.10)
				Language Test Subnormal school performance	
				fT4, continuous	
				Unadjusted	1.01 (0.92, 1.11)
				Adjusted[h]	1.04 (0.95, 1.14)
				Hypothyroxinemia	
				Unadjusted	1.41 (0.93, 2.15)
				Adjusted[h]	1.12 (0.72, 1.76)
Oken et al. (2009) [1] *Neonatal Thyroxine, Maternal Thyroid Function, and Child Cognition*	500 mother-child pairs in Massachusetts **Summary**. Neonatal total T4 levels within the euthyroid range were not predictive of cognitive outcome, nor were they associated with maternal T4 levels. Maternal thyroid function (T4, TSH, TPO Ab measured at approximately 10 GW) was not associated with any of the neurodevelopmental outcomes assessed. This study did not make an attempt to separately analyze hypothyroxinemic maternal-child pairs.	Abnormal maternal total T4 < 57,915 (4.5 µg/dL) No definition for neonates	6 mo	Visual Recognition Memory	-0.04 (-0.8, 0.7) [T4]
				Peabody Picture Vocabulary Test	-0.1 (-0.7, 0.5) [T4]
				Wide Range Assessment of Visual Motor Ability	0.004 (-0.6, 0.6) [T4]
Päkkilä et al. (2014) [2] *The Impact of Gestational Thyroid Hormone Concentration on ADHD Symptoms of the Child*	5,131 Finnish mother-child pairs (n_{cases} = 66) **Summary**. Maternal hypothyroxinemia was not significantly associated with teacher ratings of ADHD symptoms in children at 8 years of age.	fT4 < 11.4 in the first trimester fT4 < 11.1 in the second trimester	8 yr		*Odds Ratio (comparing offspring of mothers with hX and offspring of mothers without hX)*[i]
				ADHD Symptom	
				Inattention	
				-Boys	0.75 (0.33, 1.69)
				-Girls	0.66 (0.15, 2.83)

ED_005043_00079785-00063

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Hyperactivity	
				-Boys	0.69 (0.31, 1.56)
				-Girls	1.07 (0.31, 3.65)
				Rutter B2 scores ≥ 9	
				-Boys	0.75 (0.28, 1.96)
				-Girls	N/A
				Combined ADHD	
				-Boys	0.61 (0.18, 2.03)
				-Girls	N/A
Päkkilä et al. (2015) [2] *Maternal and Child's Thyroid Function and Child's Intellect and Scholastic Performance*	5,295 Finnish mother-child pairs with sufficient maternal serum samples (n_{cases} = 67) **Summary**. Female offspring of mothers with subclinical hypothyroidism had more self-evaluated difficulties in mathematics than did females of mothers with thyroid function within the population reference range. Male offspring of hypothyroxinemic mothers repeated a school class more often than did males of mothers with normal thyroid function. Male offspring of hypothyroxinemic mothers also had a higher odds of having difficulties in Finnish and/or math.	fT4 < 11.4 in the first trimester fT4 < 11.1 in the second trimester	7-8 yr and 16 yr		*Odds Ratio (comparing offspring of mothers with hX and offspring of mothers without hX)*
				Scholastic difficulties 8 yr	
				Reading (overall)	0.50 (0.18, 1.37)
				-Boys	0.47 (0.14, 1.54)
				-Girls	0.45 (0.06, 3.34)
				Writing (overall)	0.70 (0.33, 1.48)
				-Boys	0.55 (0.21, 1.42)
				-Girls	0.95 (0.28, 3.18)
				Mathematics (overall)	1.34 (0.61, 2.95)
				-Boys	1.41 (0.50, 4.03)
				-Girls	1.29 (0.38-4.32)
				Difficulties in at least one (overall)	0.85 (0.45, 1.59)
				-Boys	0.55 (0.23, 1.33)
				-Girls	1.42 (0.57, 3.55)
				Scholastic difficulties 16 yr	
				Repeated a class (overall)	**3.49 (1.06, 11.48)**

ED_005043_00079785-00064

Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				-Boys	**4.74 (1.38, 16.25)**
				-Girls	N/A
				Finnish (overall)	0.62 (0.19, 1.99)
				-Boys	0.74 (0.22, 2.48)
				-Girls	N/A
				Mathematics (overall)	1.13 (0.62, 2.09)
				-Boys	1.26 (0.54, 2.96)
				-Girls	1.08 (0.45, 2.59)
				Difficulties in Finnish or Math (overall)	1.02 (0.56, 1.85)
				-Boys	1.05 (0.46, 2.39)
				-Girls	0.99 (0.41, 2.38)
				Intellectually disabled	
				Mild (IQ between 50 and 85) (overall)	1.40 (0.34, 5.78)
				-Boys	1.63 (0.39, 6.88)
				-Girls	N/A
				Severe (overall)	N/A
				-Boys	N/A
				-Girls	N/A
				IQ ≤85 (overall)	1.08 (0.26, 4.45)
				-Boys	1.34 (0.32, 5.64)
				-Girls	N/A
				Self-evaluated scholastic difficulties in:	
				Finnish (overall)	1.23 (0.67, 2.26)
				-Boys	1.49 (0.77, 2.91)
				-Girls	0.42 (0.06, 3.05)

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Mathematics (overall)	0.99 (0.63, 1.55)
				-Boys	1.73 (0.98, 3.08)
				-Girls	0.51 (0.24, 1.07)
				Finnish and/or Math (overall)	1.20 (0.80, 1.80)
				-Boys	**2.13 (1.26, 3.62)**
				-Girls	0.54 (0.26, 1.11)
				Repeated a class (overall)	0.93 (0.23, 3.81)
				-Boys	N/A
				-Girls	1.69 (0.23, 12.73)
Román et al. (2013) [1] *Association of Gestational Maternal Hypothyroxinemia and Increased Autism Risk*	4,039 children of mothers in the Netherlands (mild hX n_{cases} = 136; severe hX n_{cases} = 159) **Summary**. Severe maternal hypothyroxinemia at a mean gestational age of 13.4 weeks was significantly associated with an almost four-fold increased risk of being a probable autistic child and a higher score on a scale of autistic symptoms among 6-year-old children	Mild: < 10th percentile (i.e., fT4 < 11.82) Severe: < 5th percentile (i.e., fT4 < 10.99)	6 yr	*Pervasive Developmental Problems*	*Logistic Regression Odds Ratio*[i]
				Borderline	
				fT4 per SD	0.93 (0.80, 1.09)
				Mild Hypothyroxinemia	1.31 (0.84, 2.04)
				Severe Hypothyroxinemia	**2.02 (1.16, 3.51)**
				Clinical	
				fT4 per SD	0.95 (0.77, 1.17)
				Mild Hypothyroxinemia	1.41 (0.78, 2.57)
				Severe Hypothyroxinemia	**2.60 (1.30, 5.18)**
				Autistic Symptoms	*Linear Regression*[i]
				Pervasive Developmental Problems	
				fT4 per SD	**-0.03 (-0.06, -0.01)**
				Mild Hypothyroxinemia	0.09 (-0.02, 0.19)
				Severe Hypothyroxinemia	**0.23 (0.07, 0.37)**

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05
				Social Responsiveness Scale	
				fT4 per SD	-0.002 (-0.01, 0.01)
				Mild Hypothyroxinemia	0.02 (-0.01, 0.04)
				Severe Hypothyroxinemia	**0.05 (0.01, 0.10)**
Suárez-Rodríguez, Julián, and Aguilar (2012) [2] *Hypothyroxinemia During Pregnancy: The Effect on Neurodevelopment in the Child*	70 Spanish mother-child pairs (n_{cases} = 37) **Summary**. Hypothyroxinemia was associated with lower scores on McCarthy Scales of Children's Abilities psychomotor developmental scales in children 38 and 60 months of age.	fT4 < 10th percentile (< 9.5)	38 and 60 mo	*McCarthy Scales*	*Difference in Mean Score*
				IGI	**-6.00 (CI NR)**
				Verbal	-2.48 (CI NR)
				Perceptual-manipulative	**-7.69 (CI NR)**
				Numerical	-1.78 (CI NR)
				Memory	**-4.41 (CI NR)**
				Motor skills	2.39 (CI NR)
van Mil et al. (2012) [2] *Maternal Hypothyroxinemia During Pregnancy and Growth of the Fetal and Infant Head*	2,621 Dutch mother-child pairs (n_{cases} = 476) **Summary**. Maternal hypothyroxinemia was associated with an increase in fetal head and infant head size. In addition, maternal hypothyroxinemia was associated with a statistically significant increased risk of cognitive delay.	fT4 < 10th percentile (11.82)	Fetal Age 13.4, 20.5, 30.3 wk) Neonatal Age 2.1 and 6.3 mo)	*Fetal and Infant Head Size*[k]	*Difference in Mean Head Circumference (mm)*
				Early Pregnancy	
				Fetal (13.4 wk)	**0.7 (0.2, 1.2)**
				Neonatal (2.1 mo)	**2.4 (1.0, 3.8)**
				Mid Pregnancy	
				Fetal (20.5 wk)	0.2 (CI NR)
				Neonatal (6.3 mo)	**2.0 (0.4, 3.5)**
				Late Pregnancy	
				Fetal (30.3 wk)	0.8 (CI NR)

CI = confidence interval; GW = gestational weeks; hX = hypothyroxinemia; NR = not reported

[a] Additional results available for ages 6, 12 and 24 months regarding auditory comprehension, expressive comprehension and total score. Readers are referred to Table 4 of Chevrier et al. (2011).

[b] All models adjusted for maternal age; income; employment status at 6 months; country of birth; Diet Quality Index; delivery complications; Peabody Picture and Vocabulary Test (PPVT) score;

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Study [Study Group]	Study Population and Summary of Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)	Age	Endpoint	Effect Estimate [β (95 % CI); fT4 measured in pmol/L; unless otherwise noted] Underlined & Bold indicate statistically significant at p < 0.05

child 5-minute Apgar score, hospitalization at 1 year; number of children in home at 1 and 2 years, home density at 2 years, family structure at 1 year; and season of assessment.

[c] All model are adjusted for age, gender, family background variables, including computer gaming time, birth order, maternal education, ethnicity, pregnancy characteristics (e.g., maternal age, BMI, diabetes, hypertension).

[d] Results marked [fT4] are across the entire range of fT4. Results marked [hX] are assuming hypothyroxinemia as an independent variable (i.e., yes/no presence of hypothyroxinemia) in the regression model. The presented results are specific for hypothyroxinemia defined as above or below the 10th percentile cut off of 7.7 pmol/L. Additional results available for <5th and 2.5th percentile in Table 4 of Finken et al. (2013).

[e] Model adjusted for child factors including gender, age and birthweight and maternal factors including age and education level.

[f] Models were adjusted for maternal age, maternal education level, maternal smoking during pregnancy, maternal prenatal distress, gestational age at blood sampling, birth weight, and child ethnicity.

[g] Adjusted for child age, sex, and ethnic background and maternal education level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, body mass index, and time of blood sampling

[h] Maternal education, ethnicity, BMI and depressive symptomatology

[i] Calculated based on logistic regression after adjusting for having more than two children in family, maternal smoking, maternal education and maternal age.

[j] Model adjusted for child's sex, ethnicity, gestational age at birth, birth weight, maternal age, educational level, smoking history, prenatal psychopathology, thyroid medication during pregnancy, parity, marital status, maternal folate, and C-reactive protein levels in early pregnancy, time of thyroid sampling during pregnancy, and paternal age.

[k] Adjusted for maternal age, BMI, height, educational level, national origin, parity, smoking, alcohol use and maternal psychopathology and fetal intra uterine position and gender. Prenatal analyses are adjusted for gestational age at assessment based on ultrasound; postnatal analyses are adjusted for infant age at assessment. Postnatal analyses are also adjusted for gestational age at birth.

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Willoughby, K., McAndrews, M. P., & Rovet, J. F. (2014). Effects of maternal hypothyroidism on offspring hippocampus and memory. *Thyroid, 24*(3), 576-584. doi:10.1089/thy.2013.0215

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ED_005043_00079785-00075

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 4/29/2019 4:12:57 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: Missing Citation in Perchlorate NPRM

Many thanks!

-----Original Message-----
From: Hernandez-Quinones, Samuel
Sent: Monday, April 29, 2019 12:05 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Missing Citation in Perchlorate NPRM

Hi Lisa,

Here are the requested Papers.

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: Christ, Lisa
Sent: Monday, April 29, 2019 11:45 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM
Importance: High

Hi Sam,
Please provide the papers requested below. Hopefully they can be easily accessed?
Thanks,
Lisa

-----Original Message-----
From: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP)
Sent: Monday, April 29, 2019 11:18 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Missing Citation in Perchlorate NPRM

Eric - See request below for three academic studies on IQ referenced in the NPRM. Could you please send me the papers when you can? Thanks.

-----Original Message-----
From: Ex. 6 DOD (PP)
Sent: Monday, April 29, 2019 9:55 AM
To: Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy (PP) >
Cc: Schwab, Margo EOP/OMB Ex. 6 DOD (PP)
Ex. 6 DOD (PP)
Subject: Missing Citation in Perchlorate NPRM

In Section 10 where EPA describes meaningful IQ differences there are 3 citations missing. At this late point instead of just asking for the citations we are requesting EPA send us electronic copies of the papers, hopefully this is possible.
Would you please ask them to forward the following?
Bellinger (2004)
Rogan and Ware (2003)
Nation and Gleaves (2001)

Message

From: Penman, Crystal [Penman.Crystal@epa.gov]
Sent: 7/7/2017 5:05:20 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]
Subject: RE: Interagency Perchlorate Peer Review Briefing with EPA

done

Crystal Penman
Program Specialist
Office of Water
Immediate Office
U.S. Environmental Protection Agency
Work: 202-564-3318
Penman.Crystal@epa.gov

From: Forsgren, Lee
Sent: Friday, July 7, 2017 1:04 PM
To: Penman, Crystal <Penman.Crystal@epa.gov>
Subject: FW: Interagency Perchlorate Peer Review Briefing with EPA

Can you respond for me.

From: Muellerleile, Caryn
Sent: Friday, July 7, 2017 11:30 AM
To: Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Margo EOP/OMB [redacted] Vlad Dorjets [redacted]
Cc: Behl, Betsy <Behl.Betsy@epa.gov>; OP ADP Calendar <OP_ADP_Calendar@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>; James_H_Kim [redacted] Barringer, Jody M. EOP/OMB [redacted] Abt, Eileen <Eileen.Abt@fda.hhs.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Moore, Beth <Beth.Moore@em.doe.gov>; [redacted] Seale, Viktoria Z. EOP/CEQ [redacted]; Bahadori, Tina <Bahadori.Tina@epa.gov>; [redacted] Kluever, April <April.Kluever@fda.hhs.gov>; Adamo, Emily (INTERN) <Emily.Adamo@em.doe.gov>; [redacted] Miller, Gregory <Miller.Gregory@epa.gov>; kevin.bromberg@sba.gov; Wirtz, Mark S <Mark.Wirtz@fda.hhs.gov>; Gavelek, Alexandra <Alexandra.Gavelek@fda.hhs.gov>
Subject: Interagency Perchlorate Peer Review Briefing with EPA

Hello all,

Just as FYI – this meeting will be cancelled and rescheduled for some time during the week of July 17. In order to make rescheduling simpler, I do not plan on cancelling the 7/10 invite until I've confirmed a new date & time.

Caryn Muellerleile
Regulatory Management Division

Office of Policy
US Environmental Protection Agency
1200 Pennsylvania Ave NW (1803A)
Washington, DC 20460
(202) 564-2855
muellerleile.caryn@epa.gov

Message

From: Bromberg, Kevin L. [kevin.bromberg@sba.gov]
Sent: 8/2/2017 1:52:00 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]
CC: 'jlaity@ Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)
Subject: FW: [Non-DoD Source] RE: Study Quality (perchlorate peer review of EPA report and associated charge questions)
Attachments: APRIL 2014 _IA-PRELIMINARY_DRAFT_MATERIALS.PDF

You now have a unanimous view from DOE, DOD (see below), SBA (us), and NASA for release of the model documentation. This is what I want to discuss with you if you have time. I understand that you want the interagency team to be satisfied with the EPA approach, but withholding the document is not helping.

Give us one week to give you whatever comments we have on the document, and it is up to EPA to make a choice as to next steps on the document. If a delay is needed, then that can be EPA's call. We are not holding up the process on the document.

I'm sure EPA can improve, if necessary, Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP) At a minimum, we'd like the opportunity to Ex. 5 Deliberative Process (DP) I'm pretty certain Ex. 5 Deliberative Process (DP) The latest discussion of study selection is found in the April 2004 Arsenic document (attached).

I also have very specific questions about the modeling that are best answered by reading the model documentation.

Please call me at Ex. 6 Personal Privacy (PP) when you get a chance.

Kevin

From: Ex. 6 Personal Privacy (PP)
Sent: Tuesday, August 01, 2017 9:37 PM
To: Linda S. (HQ-LA000) (linda.s.wennerberg@nasa.gov) Wennerberg; Bromberg, Kevin L.; Ex. 6 DOD (PP) Kim, Jim Ex. 6 Personal Privacy (PP)
Cc: Dorjets, Vlad (Ex. 6 Personal Privacy (PP) ; Ex. 6 Personal Privacy (PP) ; Moore, Beth (Beth.Moore@em.doe.gov); Ex. 6 Personal Privacy (PP)
Subject: Re: [Non-DoD Source] RE: Study Quality (perchlorate peer review of EPA report and associated charge questions)

All,
I have been incredibly busy with a number of items and have not had a chance to sound in on the numerous messages sent by our inter agency partners. But I want to make clear that DoD remains interested in providing input in the most efficient and productive way possible and we support many of the comments and requests that have been submitted thus far.

Ex. 5 Deliberative Process (DP)

Thank you,

Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Wennerberg, Linda S. (HQ-LD020)
Sent: Tuesday, August 1, 2017 4:44 PM
To: Bromberg, Kevin L.; Ex. 6 DOD (PP)
Ex. 6 DOD (PP) Kim, Jim (Ex. 6 Personal Privacy (PP)
Cc: Dorjets, Vlad (Ex. 6 Personal Privacy (PP)); 'jlaity@(Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)); Moore, Beth (Beth.Moore@em.doe.gov)
Subject: [Non-DoD Source] RE: Study Quality

All active links contained in this email were disabled. Please verify the identity of the sender, and confirm the authenticity of all links contained within the message prior to copying and pasting the address to a Web browser.

All;

Ex. 5 Deliberative Process (DP)

I understand that a meeting is being planned during the week of August 7th Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Apologies for sounding like a broken record. I look forward to the proposed face to face meeting.

Linda

Linda S. Wennerberg, Ph.D.
Environmental Management Division
NASA Headquarters
MS-2T89
300 E Street SW
Washington, DC 20546-0001

Tel: 202/358-4558
Cell: Ex. 6 Personal Privacy (PP)

Fax: 202/358-3948
linda.s.wennerberg@nasa.gov

From: Bromberg, Kevin L. [Caution-mailto:kevin.bromberg@sba.gov]
Sent: Tuesday, August 01, 2017 11:50 AM
To: Ex. 6 DOD (PP)
Ex. 6 DOD (PP) Kim, Jim Ex. 6 Personal Privacy (PP)
< Ex. 6 Personal Privacy (PP) >
Cc: Dorjets, Vlad Ex. 6 Personal Privacy (PP) >; 'jlaity@ Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) >; Moore, Beth (Beth.Moore@em.doe.gov) <Beth.Moore@em.doe.gov>;
Wennerberg, Linda S. (HQ-LD020) <linda.s.wennerberg@nasa.gov>
Subject: RE: Study Quality

Ex. 5 Deliberative Process (DP)

From: Bromberg, Kevin L.
Sent: Tuesday, August 01, 2017 11:18 AM
To: Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Kim, Jim Ex. 6 Personal Privacy (PP) < Caution-
Ex. 6 Personal Privacy (PP)
Cc: Dorjets, Vlad (Ex. 6 Personal Privacy (PP) < Ex. 6 Personal Privacy (PP)); 'jlaity Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)); Moore, Beth (Beth.Moore@em.doe.gov < Caution-
mailto:Beth.Moore@em.doe.gov >); Wennerberg, Linda S. (HQ-LA000) (linda.s.wennerberg@nasa.gov < Caution-
mailto:linda.s.wennerberg@nasa.gov >)
Subject: RE: Study Quality

Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

From: Bromberg, Kevin L.
Sent: Tuesday, August 01, 2017 11:04 AM
To: Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) Kim, Jim (Ex. 6 Personal Privacy (PP) < Caution-
r Ex. 6 Personal Privacy (PP)
Cc: Dorjets, Vlad (Ex. 6 Personal Privacy (PP) < Ex. 6 Personal Privacy (PP) ; 'jlaity@ Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP) < Caution-mailto Ex. 6 Personal Privacy (PP) >); Moore, Beth (Beth.Moore@em.doe.gov < Caution-
mailto:Beth.Moore@em.doe.gov >); Wennerberg, Linda S. (HQ-LA000) (linda.s.wennerberg@nasa.gov < Caution-
mailto:linda.s.wennerberg@nasa.gov >)
Subject: Study Quality

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) EPA Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

In short, EPA Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Appointment

From: Kim, Jim H. EOP/OMB Ex. 6 Personal Privacy EOP (PP)
Sent: 7/9/2018 3:06:32 PM
To: Kim, Jim H. EOP/OMB Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Ex. 6 DOD (PP); Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Waqar, Tayyaba [tayyaba.waqar@sba.gov]; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP Ex. 6 Personal Privacy EOP (PP); Schwab, Margo EOP/OMB Ex. 6 Personal Privacy EOP (PP); Laity, Jim A. EOP/OMB Ex. 6 Personal Privacy EOP (PP); Szabo, Aaron L. EOP/CEQ Ex. 6 Personal Privacy EOP (PP) Barringer, Jody M. EOP/OMB Ex. 6 Personal Privacy EOP (PP); Falk Curtin, Edna T. EOP/OMB Ex. 6 Personal Privacy EOP (PP) Gamache, Christopher D. EOP/OMB Ex. 6 Personal Privacy EOP (PP) Dorjets, Vlad EOP/OMB Ex. 6 Personal Privacy EOP (PP); Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fine, Leah R. EOP/OMB Ex. 6 Personal Privacy EOP (PP)

Subject: TWG - Perchlorate
Location: Conference Call

Start: 7/11/2018 6:00:00 PM
End: 7/11/2018 7:00:00 PM
Show Time As: Tentative

Recurrence: (none)

Dear Technical Working Group:

I am scheduling this conference call so that EPA can update us on their actions on regulating perchlorate in water. The external peer review of the scientific documents was completed last fall, and we have not had a recent update on the status of this activity.

Call-in Number: Ex. 6 Personal Privacy (PP)
Participants: Ex. 6 Personal Privacy (PP)

Let me know if you have questions.

Jim

Appointment

From: James_H_Kim[Ex. 6 Personal Privacy EOP (PP)]
Sent: 7/10/2018 7:02:10 PM
To: James_H_Kim@c[Ex. 6 Personal Privacy EOP (PP)]; Johnson, Ann [Johnson.Ann@epa.gov]; Nickerson, William [Nickerson.William@epa.gov]; [Ex. 6 DOD (PP)]; Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Waqar, Tayyaba [tayyaba.waqar@sba.gov]; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP [Ex. 6 Personal Privacy EOP (PP)]; Schwab, Margo EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Laity, Jim A. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Szabo, Aaron L. EOP/CEQ [Ex. 6 Personal Privacy EOP (PP)]; Barringer, Jody M. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Falk Curtin, Edna T. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Gamache, Christopher D. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fine, Leah R. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]

Subject: FW: TWG - Perchlorate
Location: Conference Call

Start: 7/11/2018 6:00:00 PM
End: 7/11/2018 7:00:00 PM
Show Time As: Busy

-----Original Appointment-----
From: James_H_Kim[Ex. 6 Personal Privacy EOP (PP)]
Sent: Monday, July 09, 2018 4:56 PM
To: James_H_Kim[Ex. 6 Personal Privacy EOP (PP)]; Nickerson, William; [Ex. 6 DOD (PP)]Wennerberg, Linda S. (HQ-LD020); Seifert, Robert; Burneson, Eric; Grevatt, Peter; Waqar, Tayyaba; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP; Schwab, Margo EOP/OMB; Laity, Jim A. EOP/OMB; Szabo, Aaron L. EOP/CEQ; Barringer, Jody M. EOP/OMB; Falk Curtin, Edna T. EOP/OMB; Gamache, Christopher D. EOP/OMB; Dorjets, Vlad EOP/OMB; Mclain, Jennifer; Fine, Leah R. EOP/OMB
Subject: FW: TWG - Perchlorate
When: Wednesday, July 11, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Conference Call

-----Original Appointment-----
From: Kim, Jim H. EOP/OMB [mailto:James_H_Kim[Ex. 6 Personal Privacy EOP (PP)]
Sent: Monday, July 09, 2018 11:07 AM
To: Kim, Jim H. EOP/OMB; [Ex. 6 DOD (PP)]Wennerberg, Linda S. (HQ-LD020); Seifert, Robert; Burneson, Eric; Grevatt, Peter; Waqar, Tayyaba; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP; Schwab, Margo EOP/OMB; Laity, Jim A. EOP/OMB; Szabo, Aaron L. EOP/CEQ; Barringer, Jody M. EOP/OMB; Falk Curtin, Edna T. EOP/OMB; Gamache, Christopher D. EOP/OMB; Dorjets, Vlad EOP/OMB; Mclain, Jennifer; Fine, Leah R. EOP/OMB
Subject: TWG - Perchlorate
When: Wednesday, July 11, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Conference Call

Dear Technical Working Group:

I am scheduling this conference call so that EPA can update us on their actions on regulating perchlorate in water. The external peer review of the scientific documents was completed last fall, and we have not had a recent update on the status of this activity.

Call-in Number: Ex. 6 Personal Privacy (PP)
Participants: Ex. 6 Personal Privacy (PP)

Let me know if you have questions.

Jim

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/28/2017 3:21:59 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Ex. 6 DOD (PP) Robert.Seifert@EM.Doe.Gov; Letitia.O'Conor@em.doe.gov; Emily.Adamo@em.doe.gov; linda.s.wennerberg@nasa.gov; tayyaba.waqar@sba.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Margo_Schwab Ex. 6 Personal Privacy EOP (PP) Gareth.Buckland@em.doe.gov; Kamela_G._White Ex. 6 Personal Privacy EOP (PP) Sarah.Jensen@Hq.Doe.Gov; Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP); Michael.Dinovi@fda.hhs.gov; Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) Annie.Lumen@fda.hhs.gov; Suzanne_Fitzpatrick [Suzanne.Fitzpatrick@fda.hhs.gov]; Eileen.Abt@fda.hhs.gov; April.Kluever@fda.hhs.gov; Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; Steve.Clark@hq.doe.gov; Beth.Moore@em.doe.gov; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP); kevin.bromberg@sba.gov; Ex. 6 DOD (PP) Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP) Mary.B.Neumayr@ Ex. 6 Personal Privacy EOP (PP) Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP) James_H_Kim Ex. 6 Personal Privacy EOP (PP); Ex. 6 DOD (PP) Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP) Ex. 6 DOD (PP) Mark.Wirtz@fda.hhs.gov; Alexandra.Gavelek@fda.hhs.gov; Gareth.Buckland@NNSA.DOE.Gov; James A. Laity Ex. 6 Personal Privacy EOP (PP); Vlad Dorjets Ex. 6 Personal Privacy EOP (PP)
CC: Kabadi, Shruti [Shruti.Kabadi@fda.hhs.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Chin, Teung [Teung.Chin@ARS.USDA.GOV]

Subject: Interagency briefing on Perchlorate Peer Review hosted by EPA
Location: EPA Headquarters East Bldg, 1201 Constitution Avenue NW, Room 2123

Start: 8/9/2017 7:00:00 PM
End: 8/9/2017 9:00:00 PM
Show Time As: Busy

EPA headquarters "East" building, entrance on Constitution Avenue between 12th & 13th at Federal Triangle, https://www.epa.gov/aboutepa/visiting-epa-headquarters

Will follow up with additional visitor instructions as needed. Conference room 2123 in the East building.

Teleconference Ex. 6 Personal Privacy (PP) access code Ex. 6 Personal Privacy (PP)

Appointment

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/10/2017 6:00:54 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Margo EOP/OMB [Margo_Schwab Ex. 6 Personal Privacy EOP (PP) Vlad Dorjets Ex. 6 Personal Privacy EOP (PP)
CC: Behl, Betsy [Behl.Betsy@epa.gov]; OP ADP Calendar [OP_ADP_Calendar@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]; Forsgren, Lee [Forsgren.Lee@epa.gov]; James_H_Kim Ex. 6 Personal Privacy EOP (PP) Barringer, Jody M. EOP/OMB Ex. 6 Personal Privacy EOP (PP); Abt, Eileen [Eileen.Abt@fda.hhs.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Moore, Beth [Beth.Moore@em.doe.gov]; Seale, Viktoria Z. EOP/CEQ Ex. 6 Personal Privacy EOP (PP); Bahadori, Tina [Bahadori.Tina@epa.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP); Kluever, April [April.Kluever@fda.hhs.gov]; Adamo, Emily (INTERN [Emily.Adamo@em.doe.gov]; Ex. 6 DOD (PP) Miller, Gregory [Miller.Gregory@epa.gov]; kevin.bromberg@sba.gov; Wirtz, Mark S [Mark.Wirtz@fda.hhs.gov]; Gavelek, Alexandra [Alexandra.Gavelek@fda.hhs.gov]; Clark, Steve [Steve.Clark@hq.doe.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Lumen, Annie [Annie.Lumen@fda.hhs.gov]; Ex. 6 DOD (PP) Ex. 6 DOD (PP) Dinovi, Michael J [Michael.Dinovi@fda.hhs.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Suzanne_Fitzpatrick [Suzanne.Fitzpatrick@fda.hhs.gov]; Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Nasir, Iqra [nasir.iqra@epa.gov]; Smegal, Deborah [Deborah.Smegal@fda.hhs.gov]

Subject: FW: Interagency Perchlorate Peer Review Briefing with EPA (rescheduled)
Location: teleconference Ex. 6 Personal Privacy (PP) / access code Ex. 6 Personal Privacy (PP)

Start: 7/18/2017 6:00:00 PM
End: 7/18/2017 7:00:00 PM
Show Time As: Busy

Appointment

From: James_H_Kim [Ex. 6 Personal Privacy EOP (PP)]
Sent: 7/9/2018 8:56:05 PM
To: James_H_Kim [Ex. 6 Personal Privacy EOP (PP)]; Nickerson, William [Nickerson.William@epa.gov]; Ex. 6 DOD (PP); Ex. 6 DOD (PP); Wennerberg, Linda S. (HQ-LD020) [linda.s.wennerberg@nasa.gov]; Seifert, Robert [Robert.Seifert@EM.Doe.Gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Grevatt, Peter [Grevatt.Peter@epa.gov]; Waqar, Tayyaba [tayyaba.waqar@sba.gov]; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP [Ex. 6 Personal Privacy EOP (PP)]; Schwab, Margo EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Laity, Jim A. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Szabo, Aaron L. EOP/CEQ [Ex. 6 Personal Privacy EOP (PP)]; Barringer, Jody M. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Falk Curtin, Edna T. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Gamache, Christopher D. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Dorjets, Vlad EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]; Mclain, Jennifer [Mclain.Jennifer@epa.gov]; Fine, Leah R. EOP/OMB [Ex. 6 Personal Privacy EOP (PP)]

Subject: FW: TWG - Perchlorate
Location: Conference Call

Start: 7/11/2018 6:00:00 PM
End: 7/11/2018 7:00:00 PM
Show Time As: Busy

-----Original Appointment-----
From: Kim, Jim H. EOP/OMB [mailto: Ex. 6 Personal Privacy EOP (PP)]
Sent: Monday, July 09, 2018 11:07 AM
To: Kim, Jim H. EOP/OMB; Ex. 6 DOD (PP); Wennerberg, Linda S. (HQ-LD020); Seifert, Robert; Burneson, Eric; Grevatt, Peter; Waqar, Tayyaba; kevin.bromberg@sba.gov; Brenner, Sara A. EOP/OSTP; Schwab, Margo EOP/OMB; Laity, Jim A. EOP/OMB; Szabo, Aaron L. EOP/CEQ; Barringer, Jody M. EOP/OMB; Falk Curtin, Edna T. EOP/OMB; Gamache, Christopher D. EOP/OMB; Dorjets, Vlad EOP/OMB; Mclain, Jennifer; Fine, Leah R. EOP/OMB
Subject: TWG - Perchlorate
When: Wednesday, July 11, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Conference Call

Dear Technical Working Group:

I am scheduling this conference call so that EPA can update us on their actions on regulating perchlorate in water. The external peer review of the scientific documents was completed last fall, and we have not had a recent update on the status of this activity.

Call-in Number: Ex. 6 Personal Privacy (PP)
Participants: Ex. 6 Personal Privacy (PP)

Let me know if you have questions.

Jim

Message

From: Johnson, Ann [Johnson.Ann@epa.gov]
Sent: 6/7/2018 4:11:56 PM
To: Nickerson, William [Nickerson.William@epa.gov]
Subject: FW: EPA Perchlorate Peer Review Report

This is the email I was referring to regarding the March peer review report (Versar). I didn't hit send.

From: Burneson, Eric
Sent: Thursday, April 5, 2018 10:01 AM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) 'Robert.Seifert@EM.Doe.Gov' <Robert.Seifert@EM.Doe.Gov>; 'August, Lisa L. EOP/OMB' < Ex. 6 Personal Privacy EOP (PP) >; O'Conor, Letitia <Letitia.O'Conor@em.doe.gov>; 'Emily.Adamo@em.doe.gov' <Emily.Adamo@em.doe.gov>; 'linda.s.wennerberg@nasa.gov' <linda.s.wennerberg@nasa.gov>; 'tayyaba.waqar@sba.gov' <tayyaba.waqar@sba.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) 'Margo_Schwab Ex. 6 Personal Privacy EOP (PP) >; 'Gareth.Buckland@em.doe.gov' <Gareth.Buckland@em.doe.gov>; 'Kamela_G._White Ex. 6 Personal Privacy EOP (PP) < Ex. 6 Personal Privacy EOP (PP) >; 'Sarah.Jensen@Hq.Doe.Gov' <Sarah.Jensen@Hq.Doe.Gov>; 'Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP) >; 'Michael.Dinovi@fda.hhs.gov' <Michael.Dinovi@fda.hhs.gov>; 'Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) >; 'Annie.Lumen@fda.hhs.gov' <Annie.Lumen@fda.hhs.gov>; Suzanne_Fitzpatrick <Suzanne.Fitzpatrick@fda.hhs.gov>; 'Eileen.Abt@fda.hhs.gov' <Eileen.Abt@fda.hhs.gov>; 'April.Kluever@fda.hhs.gov' <April.Kluever@fda.hhs.gov>; Jeff Fisher <Jeffrey.Fisher@fda.hhs.gov>; 'Steve.Clark@hq.doe.gov' <Steve.Clark@hq.doe.gov>; 'Beth.Moore@em.doe.gov' <Beth.Moore@em.doe.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) 'Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) ; kevin.bromberg@sba.gov; Ex. 6 Personal Privacy (PP) 'Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP) >; 'Mary.B.Neumayr Ex. 6 Personal Privacy EOP (PP) < Ex. 6 Personal Privacy EOP (PP) >; 'Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP) >; James_H_Kim Ex. 6 Personal Privacy EOP (PP) ' Ex. 6 Personal Privacy (PP) 'Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP) < Ex. 6 Personal Privacy EOP (PP) >; Ex. 6 Personal Privacy (PP) >; 'Mark.Wirtz@fda.hhs.gov' <Mark.Wirtz@fda.hhs.gov>; 'Alexandra.Gavelek@fda.hhs.gov' <Alexandra.Gavelek@fda.hhs.gov>; 'Gareth.Buckland@NNSA.DOE.Gov' <Gareth.Buckland@NNSA.DOE.Gov>; 'James A. Laity' < Ex. 6 Personal Privacy EOP (PP) ; 'Vlad Dorjets (Ex. 6 Personal Privacy EOP (PP) 'Kabadi, Shruti' <Shruti.Kabadi@fda.hhs.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; 'Chin, Teung' <Teung.Chin@ARS.USDA.GOV>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; 'Kunickis, Sheryl - OSEC' <Sheryl.Kunickis@osec.usda.gov>; 'Jensen, Michael C. EOP/CEQ' < Ex. 6 Personal Privacy EOP (PP) Corrales, Mark <Corrales.Mark@epa.gov>; 'Domesle, Alexander - ARS' <Alexander.Domesle@ARS.USDA.GOV>; DCRoomEast2123/DC-ICC-OW-OGWDW <DCRoomEast2123@epa.gov>; Ex. 6 Personal Privacy (PP) ; 'Robert.Seifert@EM.Doe.Gov' <Robert.Seifert@EM.Doe.Gov>; 'August, Lisa L. EOP/OMB' < Ex. 6 Personal Privacy EOP (PP) >; O'Conor, Letitia <Letitia.O'Conor@em.doe.gov>; 'Emily.Adamo@em.doe.gov' <Emily.Adamo@em.doe.gov>; 'linda.s.wennerberg@nasa.gov' <linda.s.wennerberg@nasa.gov>; 'tayyaba.waqar@sba.gov' <tayyaba.waqar@sba.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) Margo_Schwab Ex. 6 Personal Privacy EOP (PP) >; 'Gareth.Buckland@em.doe.gov' <Gareth.Buckland@em.doe.gov>; 'Kamela_G._White Ex. 6 Personal Privacy EOP (PP)

<Ex. 6 Personal Privacy EOP (PP)>; 'Sarah.Jensen@Hq.Doe.Gov' <Sarah.Jensen@Hq.Doe.Gov>; 'Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP) 'Michael.Dinovi@fda.hhs.gov' <Michael.Dinovi@fda.hhs.gov>; 'Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) 'Annie.Lumen@fda.hhs.gov' <Annie.Lumen@fda.hhs.gov>; 'Eileen.Abt@fda.hhs.gov' <Eileen.Abt@fda.hhs.gov>; 'April.Kluever@fda.hhs.gov' <April.Kluever@fda.hhs.gov>; 'Steve.Clark@hq.doe.gov' <Steve.Clark@hq.doe.gov>; 'Beth.Moore@em.doe.gov' <Beth.Moore@em.doe.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); 'Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) <Ex. 6 Personal Privacy EOP (PP)>; Ex. 6 Personal Privacy (PP) 'Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP)' <Mary.B.Neumayr Ex. 6 Personal Privacy EOP (PP)>; 'Jennifer_M_Lee Ex. 6 Personal Privacy EOP (PP)>; Ex. 6 Personal Privacy (PP) 'Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP)>; Ex. 6 Personal Privacy (PP) 'Mark.Wirtz@fda.hhs.gov' <Mark.Wirtz@fda.hhs.gov>; 'Alexandra.Gavelek@fda.hhs.gov' <Alexandra.Gavelek@fda.hhs.gov>; 'Gareth.Buckland@NNSA.DOE.Gov' <Gareth.Buckland@NNSA.DOE.Gov>; 'James A. Laity' <Ex. 6 Personal Privacy EOP (PP)> 'Vlad Dorjets Ex. 6 Personal Privacy EOP (PP)>; 'Kabadi, Shruti' <Shruti.Kabadi@fda.hhs.gov>; 'Chin, Teung' <Teung.Chin@ARS.USDA.GOV>; 'Kunickis, Sheryl - OSEC' <Sheryl.Kunickis@osec.usda.gov>; 'Jensen, Michael C. EOP/CEQ' <Ex. 6 Personal Privacy EOP (PP)>; 'Domesle, Alexander - ARS' <Alexander.Domesle@ARS.USDA.GOV>; Ex. 6 Personal Privacy (PP); 'Robert.Seifert@EM.Doe.Gov' <Robert.Seifert@EM.Doe.Gov>; 'August, Lisa L. EOP/OMB' <Ex. 6 Personal Privacy EOP (PP)>; O'Conor, Letitia <Letitia.O'Conor@em.doe.gov>; 'Emily.Adamo@em.doe.gov' <Emily.Adamo@em.doe.gov>; 'linda.s.wennerberg@nasa.gov' <linda.s.wennerberg@nasa.gov>; 'tayyaba.waqar@sba.gov' <tayyaba.waqar@sba.gov>; Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP); 'Margo_Schwab Ex. 6 Personal Privacy EOP (PP)>; 'Gareth.Buckland@em.doe.gov' <Gareth.Buckland@em.doe.gov>; 'Ex. 6 Personal Privacy EOP (PP) <Kamela_G._White Ex. 6 Personal Privacy EOP (PP)>; 'Sarah.Jensen@Hq.Doe.Gov' <Sarah.Jensen@Hq.Doe.Gov>; 'Jody_M._Barringer Ex. 6 Personal Privacy EOP (PP)>; 'Michael.Dinovi@fda.hhs.gov' <Michael.Dinovi@fda.hhs.gov>; 'Edna_F._Curtin Ex. 6 Personal Privacy EOP (PP) 'Annie.Lumen@fda.hhs.gov' <Annie.Lumen@fda.hhs.gov>; 'Eileen.Abt@fda.hhs.gov' <Eileen.Abt@fda.hhs.gov>; 'April.Kluever@fda.hhs.gov' <April.Kluever@fda.hhs.gov>; 'Steve.Clark@hq.doe.gov' <Steve.Clark@hq.doe.gov>; 'Beth.Moore@em.doe.gov' <Beth.Moore@em.doe.gov>; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP) 'Andrea_L_Grossman Ex. 6 Personal Privacy EOP (PP) <Ex. 6 Personal Privacy EOP (PP)> Ex. 6 Personal Privacy (PP) 'Christopher_D_Gamache Ex. 6 Personal Privacy EOP (PP)>; 'Mary.B.Neumayr Ex. 6 Personal Privacy EOP (PP) <Ex. 6 Personal Privacy EOP (PP)>; 'Jennifer_M_Lee@ Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy EOP (PP)>; Ex. 6 Personal Privacy (PP); 'Viktoria.Z.Seale Ex. 6 Personal Privacy EOP (PP)>; Ex. 6 Personal Privacy (PP); 'Mark.Wirtz@fda.hhs.gov' <Mark.Wirtz@fda.hhs.gov>; 'Alexandra.Gavelek@fda.hhs.gov' <Alexandra.Gavelek@fda.hhs.gov>; 'Gareth.Buckland@NNSA.DOE.Gov' <Gareth.Buckland@NNSA.DOE.Gov>; 'James A. Laity' <Ex. 6 Personal Privacy EOP (PP)>; 'Vlad Dorjets Ex. 6 Personal Privacy EOP (PP); 'Kabadi, Shruti' <Shruti.Kabadi@fda.hhs.gov>; 'Chin, Teung' <Teung.Chin@ARS.USDA.GOV>; 'Kunickis, Sheryl - OSEC' <Sheryl.Kunickis@osec.usda.gov>; 'Jensen, Michael C. EOP/CEQ' <Ex. 6 Personal Privacy EOP (PP)>; 'Domesle, Alexander - ARS' <Alexander.Domesle@ARS.USDA.GOV>

Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>

Subject: EPA Perchlorate Peer Review Report

Federal Partners:

As you are aware, the external Peer Review for EPA's "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", took place on January 29 and 30, 2018.

I am writing to inform you that the Final Peer Review Report is publicly available in the Perchlorate docket at https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0439-0012 .

EPA will consider the recommendations and observations from the panelists and public comment as we continue our regulatory decision making in accordance with the Safe Drinking Water Act. As we have discussed previously, any

perchlorate regulatory actions and supporting analysis will undergo formal Inter-Agency review. Thank you for your continued interest and input on this important issue.

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

Appointment

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 11/6/2017 3:55:44 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP); Lavoie, Emma [Lavoie.Emma@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
CC: Ex. 6 Personal Privacy (PP) Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)

Subject: Perchlorate BBDR questions
Location: Teleconfernce Ex. 6 Personal Privacy (PP)

Start: 11/8/2017 4:00:00 PM
End: 11/8/2017 5:00:00 PM
Show Time As: Busy

Ex. 6 Personal Privacy (PP)

We propose a conference call to discuss the BBDR modeling issue Ex. 6 Personal Privacy (PP) identified in issue number 1 below. Please accept this invitation if this time works for you. (we have an alternative time on Nov. 7 at 3:00 pm). Thanks and we look forward to speaking with you.

Eric Burneson

From: Ex. 6 Personal Privacy (PP)
Sent: Thursday, November 02, 2017 8:47 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Ex. 6 Personal Privacy (PP)
Subject: FW: Perchlorate questions for Paul

Eric, See below with respect with what we would like to ask Paul Schlosser about the perchlorate model. Thanks, Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Wednesday, November 1, 2017 4:08 PM
To: Ex. 6 Personal Privacy (PP)
Subject: Perchlorate questions for Paul

Ex. 6 Personal Privacy (PP)

Sorry this is later than you wanted, but it is taking me time to wrap my head around the concepts again. I would like to see if Paul can provide these simulations...and they refer back to our discussions last week about just focusing on perchlorate's known mechanism of action:

1. The simulation of serum perchlorate are good, however just to confirm that the model accurately simulates iodide uptake and perchlorate induced inhibition of of uptake, it would be nice to actually see some simulations of Greer's 2002 radioiodide uptake in the thyroid data, under normal iodide uptake and following perchlorate.

2. This second comment may be hard to understand and I would welcome any questions Paul or anyone would have about my comment.

Figure A-56 is somewhat misleading. It is not clear to what degree that the highter radioiodide uptake is due to just the higher specific activity of the radioiodide in the blood because the blood concentration is less diluted with cold iodide in the subjects with lower iodide intake. If you could simulate the thyroid cold iodide concentration for each of the iodide intakes measured in Delange 2000 data and then plot the ratio of radioiodide/cold iodide for each of those points, the data would look flatter. It would reflect the thyroid hormone data in Figures A54 and A55 better, which appears to be very flat, show high reliance of humans to low dietary iodide.

Ex. 6 Personal Privacy (PP)

Message

From: Lavoie, Emma [Lavoie.Emma@epa.gov]
Sent: 11/8/2017 3:32:32 AM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]
CC: Schlosser, Paul [Schlosser.Paul@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Hauchman, Fred [hauchman.fred@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; Huff, Lisa [Huff.Lisa@epa.gov]
Subject: RE: Perchlorate questions for Paul

Very good.

-Emma

Tel: Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric
Sent: Tuesday, November 07, 2017 4:00 PM
To: Lavoie, Emma <Lavoie.Emma@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate questions for Paul

Emma:
Thank you for sharing the memo with responses to the DOD questions. I don't have any questions about these responses. My only request is that in the course of the conversation with DOD I would rather not commit definitively to what will be in the presentation to the peer reviewers. I am concerned that we still have a number of other issues that may be raised in public comments that we may also have to respond to or clarify in the presentations. Therefore I would prefer to state that we will consider this and other comments as we put our presentations together.

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

-----Original Message-----
From: Lavoie, Emma
Sent: Tuesday, November 07, 2017 11:29 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>
Subject: RE: Perchlorate questions for Paul

Hello Eric,

Attached is a memo from Paul responding to the questions from DoD. This is for EPA use only. We are happy to provide related verbal input on phone to DoD tomorrow. Please take a look and let us know if you have questions.

Paul would provide some of the information at the peer review meeting, i.e., response to the first question and possibly the later part of response to second question. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

-Emma

Tel: Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric
Sent: Thursday, November 02, 2017 9:52 AM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: FW: Perchlorate questions for Paul

Dave and Victor: See the questions/requests below. #1 does appear to be a request for additional simulations. Please advise if these are issues that are best discussed in a conference call and if so please identify 2 or 3 dates and times when critical participants would be available

Thanks in advance for your assistance with this

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

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Thursday, November 02, 2017 8:47 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Ex. 6 Personal Privacy (PP)
Subject: FW: Perchlorate questions for Paul

Eric, See below with respect with what we would like to ask Paul Schlosser about the perchlorate model.
Thanks, Dave

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Wednesday, November 1, 2017 4:08 PM
To: Ex. 6 Personal Privacy (PP)
Subject: Perchlorate questions for Paul

Ex. 6 Personal Privacy (PP)

Sorry this is later than you wanted, but it is taking me time to wrap my head around the concepts again. I would like to see if Paul can provide these simulations...and they refer back to our discussions last week about just focusing on perchlorate's known mechanism of action:

1. The simulation of serum perchlorate are good, however just to confirm that the model accurately simulates iodide uptake and perchlorate induced inhibition of of uptake, it would be nice to actually see some simulations of Greer's 2002 radioiodide uptake in the thyroid data, under normal iodide uptake and following perchlorate.

2. This second comment may be hard to understand and I would welcome any questions Paul or anyone would have about my comment.

Figure A-56 is somewhat misleading. It is not clear to what degree that the highter radioiodide uptake is due to just the higher specific activity of the radioiodide in the blood because the blood concentration is less diluted with cold iodide in the subjects with lower iodide intake. If you could simulate the thyroid cold iodide concentration for each of the iodide intakes measured in Delange 2000 data and then plot the ratio of radioiodide/cold iodide for each of those points, the data would look flatter. It would reflect the thyroid hormone data in Figures A54 and A55 better, which appears to be very flat, show high reliance of humans to low dietary iodide.

Ex. 6 Personal Privacy (PP)

F
C Ex. 6 Personal Privacy (PP)

Message

From: Lavoie, Emma [Lavoie.Emma@epa.gov]
Sent: 11/3/2017 8:09:09 PM
To: Burneson, Eric [Burneson.Eric@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]
Subject: RE: Perchlorate questions for Paul

Hi Eric,

We have asked Paul to write a short note for you to share with DoD on how to run the greer test in the model (answers question 1). We feel that would be a quick response and time for phone call is not necessary.
Paul has also run some data per question 1 and is willing to present it at his presentation at the peer review meeting.

-Emma

Tel: Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Burneson, Eric
Sent: Thursday, November 02, 2017 3:57 PM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Lavoie, Emma <Lavoie.Emma@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: RE: Perchlorate questions for Paul

Thanks David:
I just spoke to Emma and appreciate the concerns with the second question. I think that we can respond that we have no questions or comments on Elaine's potential comment on the report and encourage them to provide it to the docket for the peer reviewers to consider. I will wait to hear back from you before closing the loop with DOD.
Eric

-----Original Message-----
From: Bussard, David
Sent: Thursday, November 02, 2017 3:38 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Lavoie, Emma <Lavoie.Emma@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: RE: Perchlorate questions for Paul

Eric,

Thanks. We want to do some internal checks, but
- looks like we are comfortable responding on the first question.
- not clear we should or want to engage now on second question.

David

-----Original Message-----
From: Burneson, Eric
Sent: Thursday, November 02, 2017 9:52 AM
To: Bussard, David <Bussard.David@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: FW: Perchlorate questions for Paul

Dave and Victor: See the questions/requests below. #1 does appear to be a request for additional simulations. Please advise if these are issues that are best discussed in a conference call and if so please identify 2 or 3 dates and times when critical participants would be available

Thanks in advance for your assistance with this

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

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Thursday, November 02, 2017 8:47 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Ex. 6 Personal Privacy (PP)
Subject: FW: Perchlorate questions for Paul

Eric, See below with respect with what we would like to ask Paul Schlosser about the perchlorate model.
Thanks, Dave

Ex. 6 Personal Privacy (PP)

-----Original Message-----
From: Ex. 6 Personal Privacy (PP)
Sent: Wednesday, November 1, 2017 4:08 PM
To: Ex. 6 Personal Privacy (PP)
Subject: Perchlorate questions for Paul

Ex. 6 Personal Privacy (PP)

Sorry this is later than you wanted, but it is taking me time to wrap my head around the concepts again. I would like to see if Paul can provide these simulations...and they refer back to our discussions last week about just focusing on perchlorate's known mechanism of action:

1. The simulation of serum perchlorate are good, however just to confirm that the model accurately simulates iodide uptake and perchlorate induced inhibition of of uptake, it would be nice to actually see some simulations of Greer's 2002 radioiodide uptake in the thyroid data, under normal iodide uptake and following perchlorate.

2. This second comment may be hard to understand and I would welcome any questions Paul or anyone would have about my comment.

Figure A-56 is somewhat misleading. It is not clear to what degree that the highter radioiodide uptake is due to just the higher specific activity of the radioiodide in the blood because the blood concentration is less diluted with cold iodide in the subjects with lower iodide intake. If you could simulate the thyroid cold iodide concentration for each of the iodide intakes measured in Delange 2000 data and then plot the ratio of radioiodide/cold iodide for each of those points, the data would look flatter. It would reflect the thyroid hormone data in Figures A54 and A55 better, which appears to be very flat, show high reliance of humans to low dietary iodide.

Ex. 6 Personal Privacy (PP)

Message

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 7/5/2017 5:45:33 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]
Subject: RE: Perchlorate Peer Review Briefing with EPA

Thanks. I'll send the options for next week over to OMB.

From: Christ, Lisa
Sent: Wednesday, July 05, 2017 1:44 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hi Caryn,
Ex. 6 Personal Privacy (PP) next week, so you should not try to work around me. Eric Burneson is probably most critical to attend.
Lisa

From: Muellerleile, Caryn
Sent: Wednesday, July 05, 2017 1:31 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hello Lisa,

In trying to look ahead to schedule another meeting with interagency counterparts, I was trying to look into something for next week, but you might be out? If there is desire to move ahead with this meeting regardless, I have these dates/times on offer for OMB:

Mon. 7/10 from 10-11 or 2-3
Wed. 7/12 from 10-11

Otherwise, the next widely available date for many of the OW participants seemed to be 7/19 (Wed) from 10-11 or 3-4.

What do you think?

Caryn

From: Muellerleile, Caryn
Sent: Friday, June 16, 2017 8:53 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hello Lisa,

OMB has indicated a preference for 6/29/17 (Thurs) 3-4. Can you help us out with a call-in number?

Caryn

From: Christ, Lisa
Sent: Wednesday, June 14, 2017 4:50 PM

To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hi Caryn,
Please see my responses below. Let me know if you have questions or need anything else.

Thanks,
Lisa

From: Muellerleile, Caryn
Sent: Wednesday, June 14, 2017 11:09 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: FW: Perchlorate Peer Review Briefing with EPA

Hello Lisa,

Thanks again for all of the helpful information you provided a few moments ago on the telephone. Before we engage with other federal partners on this meeting, I want to see if between us we can clarify a few things:

1) If the peer review is under a consent decree for action by October, EPA should act on this publication/public comment in early July, such that this courtesy meeting should happen between now and the end of June. Would you characterize that as correct, or should it be worded differently?
The perchlorate SDWA action has deadlines that are established under a consent decree. The first consent decree deadline is for completion of the expert peer review by October 18, 2017 of materials to inform EPA's SDWA action on perchlorate. While this is a unenforceable date, the EPA would need to file a letter with the court explaining why we did not meet the deadline. The consent decree also established enforceable deadlines of October 2018 for a proposal and December 2019 for final. Delay in completing the expert peer review will severely limit the timeframe for EPA to develop a proposal.

2) Any of the individuals, EPA or non, listed below who you are aware should NOT be invited, please let us know.
No exclusions I'm aware of.
3) For logistics, should we even provide a webinar link, or just a call-in number and assume that we'll provide attachments for discussion once those are available? Whose call-in is preferred, OW or OP? We can host a line as needed.
We can set up a webinar if OMB and federal partners are able to access Adobe connect. If that's an issue, we can provide the presentation as a pdf document. OW can provide a call in number.

4) Does OW have any preference on dates/times? It is typically helpful to have a few suggestions ready to go when contacting Vlad. Also, who are the OW 'must have' and who are the 'optional' attendees?
Potential dates:
Th June 29; 11am-noon or 3pm-4pm
M July 3; 10am-11am or 11am-noon
F June 30; 9am-10am

Must: Grevatt, Peter; Burneson, Eric; Olson, Daniel; Christ, Lisa; Hafez, Ahmed; Strong, Jamie; McLain, Jennifer
Optional: Behl, Betsy

Thanks for all of your assistance!
Caryn
564-2855

-----Original Appointment-----
From: Muellerleile, Caryn [mailto:Muellerleile.Caryn@epa.gov]

Sent: Thursday, September 22, 2016 3:02 PM
To: Muellerleile, Caryn; Laity, Jim A. EOP/OMB; Dorjets, Vlad EOP/OMB; Kim, Jim H. EOP/OMB; Schwab, Margo EOP/OMB; Grevatt, Peter; Burneson, Eric; Olson, Daniel; Christ, Lisa; Schlosser, Paul; Flowers, Lynn; Strong, Jamie; Johnson, Ann; Wiggins, Lanelle
Cc: Behl, Betsy; OP ADP Calendar; Owens, Nicole; Adamo, Emily (INTERN); Wennerberg, Linda S. (HQ-LD020); White, Kamela G. EOP/OMB; Ex. 6 Personal Privacy (PP); Seifert, Robert; O'Conor, Letitia; Buckland, Gareth; Jensen, Sarah; Ex. 6 Personal Privacy (PP) Rodan, Bruce D. EOP/OSTP; Barringer, Jody M. EOP/OMB; Bertrand, Charlotte
Subject: Perchlorate Peer Review Briefing with EPA
When: Tuesday, September 27, 2016 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Ex. 6 Personal Privacy (PP)

Update: please access online presentation from EPA at
Ex. 6 Personal Privacy (PP)

Call-in remains the same: Ex. 6 Personal Privacy (PP)

Message

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 6/14/2017 3:09:18 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]
Subject: FW: Perchlorate Peer Review Briefing with EPA

Hello Lisa,

Thanks again for all of the helpful information you provided a few moments ago on the telephone. Before we engage with other federal partners on this meeting, I want to see if between us we can clarify a few things:

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4) Does OW have any preference on dates/times? It is typically helpful to have a few suggestions ready to go when contacting Vlad. Also, who are the OW 'must have' and who are the 'optional' attendees?

Thanks for all of your assistance!
Caryn
564-2855

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From: Muellerleile, Caryn [mailto:Muellerleile.Caryn@epa.gov]
Sent: Thursday, September 22, 2016 3:02 PM
To: Muellerleile, Caryn; Laity, Jim A. EOP/OMB; Dorjets, Vlad EOP/OMB; Kim, Jim H. EOP/OMB; Schwab, Margo EOP/OMB; Grevatt, Peter; Burneson, Eric; Olson, Daniel; Christ, Lisa; Schlosser, Paul; Flowers, Lynn; Strong, Jamie; Johnson, Ann; Wiggins, Lanelle
Cc: Behl, Betsy; OP ADP Calendar; Owens, Nicole; Adamo, Emily (INTERN); Wennerberg, Linda S. (HQ-LD020); White, Kamela G. EOP/OMB; Ex. 6 Personal Privacy (PP) Seifert, Robert; O'Conor, Letitia; Buckland, Gareth; Jensen, Sarah; Ex. 6 Personal Privacy (PP) Rodan, Bruce D. EOP/OSTP; Barringer, Jody M. EOP/OMB; Bertrand, Charlotte
Subject: Perchlorate Peer Review Briefing with EPA
When: Tuesday, September 27, 2016 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: conference line Ex. 6 Personal Privacy (PP)

Update: please access online presentation from EPA at
Ex. 6 Personal Privacy (PP)

Call-in remains the same: Ex. 6 Personal Privacy (PP)

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 6/19/2017 2:46:32 PM
To: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]; Nurse, Leanne [Nurse.Leanne@epa.gov]
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hi Caryn,
We can use Eric's.
Ex. 6 Personal Privacy (PP)

Lisa

From: Muellerleile, Caryn
Sent: Monday, June 19, 2017 10:32 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hello Lisa,

Do you have a call-in number that you can provide?

Thanks,
Caryn

From: Christ, Lisa
Sent: Wednesday, June 14, 2017 4:50 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: RE: Perchlorate Peer Review Briefing with EPA

Hi Caryn,
Please see my responses below. Let me know if you have questions or need anything else.

Thanks,
Lisa

From: Muellerleile, Caryn
Sent: Wednesday, June 14, 2017 11:09 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: FW: Perchlorate Peer Review Briefing with EPA

Hello Lisa,

Thanks again for all of the helpful information you provided a few moments ago on the telephone. Before we engage with other federal partners on this meeting, I want to see if between us we can clarify a few things:

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Optional: Behl, Betsy

Thanks for all of your assistance!
Caryn
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Cc: Behl, Betsy; OP ADP Calendar; Owens, Nicole; Adamo, Emily (INTERN); Wennerberg, Linda S. (HQ-LD020); White, Kamela G. EOP/OMB; Ex. 6 Personal Privacy (PP) Seifert, Robert; O'Conor, Letitia; Buckland, Gareth; Jensen, Sarah; Ex. 6 Personal Privacy (PP); Rodan, Bruce D. EOP/OSTP; Barringer, Jody M. EOP/OMB; Bertrand, Charlotte
Subject: Perchlorate Peer Review Briefing with EPA
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