OGWDW Bi-Weekly with OW

December 10, 2019

Agenda

- Lead Free Plumbing Materials – OMB Significance Determination
- Regulatory Determinations for CCL 4 – OMB review
- NDWAC Consultations – LCR Revisions and Perchlorate
- Water Workforce Initiative
- WIIN Grant RFA – Option Selection for the ADM
- National Governors Association Annual Water Policy Meeting

Message

From: Flowers, Lynn [Flowers.Lynn@epa.gov]
Sent: 8/7/2017 8:46:28 PM
To: Bussard, David [Bussard.David@epa.gov]
CC: Burneson, Eric [Burneson.Eric@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]
Subject: RE: Perchlorate charge

Thanks David. I am working on a new draft version of the charge and also have responses to comments on the OMB suggested edits. I will forward asap.

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Policy
US EPA
Washington, DC
202-564-6293

From: Bussard, David
Sent: Monday, August 07, 2017 4:32 PM
To: Flowers, Lynn <Flowers.Lynn@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: RE: Perchlorate charge

Thanks,

I just did a quick read through. Some of the OMB changes look fine, or look like reasonable starting points. I think there was only one, perhaps two, I thought we should flat reject.

We can talk tomorrow, but to jump start discussion, I made some comment-bubble observations embedded in attached.

David

> **From:** Flowers, Lynn
> **Sent:** Monday, August 07, 2017 3:58 PM
> **To:** Bussard, David <Bussard.David@epa.gov>
> **Cc:** Burneson, Eric <Burneson.Eric@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
> **Subject:** FW: Perchlorate charge
>
> Just getting this to David. I propose that we talk in the morning. I can set something up. David, Eric, Lisa H., Lisa C., Greg and Ahmed?
> I'll finish up what I was doing to edit and send and then let's talk in the morning. I can make edits as we talk. OK?
>
> Lynn Flowers, PhD, DABT
> Associate Director for Science
> Office of Science Policy
> US EPA
> Washington, DC
> 202-564-6293

From: Kim, Jim H. EOP/OMB [mailto Ex. 6 Personal Privacy (PP)
Sent: Monday, August 07, 2017 3:45 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>
Cc: Schwab, Margo 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: Perchlorate charge

Hi Caryn, Eric and Lynn,

Thank you for your patience as we worked on this. Attached is a version of the charge with our suggestions in tracked changes. Please let me know if you have any questions.

Best regards,
Jim

James Kim, Ph.D., DABT
Office of Management and Budget
202-395-3085
Ex. 6 Personal Privacy (PP)

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What is an adverse effect? A possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity ☆

David C. Bellinger*

Children's Hospital Boston, Neuroepidemiology Unit, Harvard Medical School, Farley Basement Box 127, 300 Longwood Avenue, Boston, MA 02115 USA

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Abstract

The sizes of the effects observed in studies that rely on neurobehavioral endpoints are often small. Because the mean deficits implied are more modest in magnitude than are those that correspond to the clinical criteria used to diagnose "disease," some observers dismiss them as inconsequential. Other observers argue that the mean deficits take on greater import when viewed as effects on a population rather than on individual members of the population. Several considerations germane to an effort to reconcile these perspectives are discussed: (1) the relative sensitivity of clinical diagnoses and continuously distributed scores on neurobehavioral tests as indices of adverse effect, (2) the syndromal nature of many diagnoses in pediatric neurology and neuropsychology and the implications of shifting nosology, (3) neurobehavioral test-score changes as surrogates or as prodromes for clinically significant deficits, (4) the distinction between individual risk and population risk, and (5) the tendency of the distribution of a risk factor in a population to move up and down as a whole. The clinical and epidemiological perspectives are complementary rather than incompatible.
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Keywords: Epidemiology; Toxicology; Neurobehavior; Population; Risk assessment

1. Introduction

None of the steps of a risk assessment is more momentous than the definition of the critical adverse effect. An assumption that underlies the definition is that reducing the prevalence of the effect will improve the health of a population. If it would not, then an exposure standard that relies on it as a point of departure will be unnecessarily restrictive. If the definition of an adverse effect underestimates the morbidity associated with an exposure, however, the standard will be insufficiently protective.

The issue is particularly vexing with respect to studies of the impact of community exposures to neurotoxicants, where concern lies with the lower end of the dose–response relationship and where putative effects, if any, will be subtle. Suppose that, compared to children with values on a biomarker of exposure that place them in the lowest quartile, children with biomarker values in the highest quartile show, on average, a decrement of 3 points in mean full-scale Intelligence Quotient (IQ), require 100 ms longer to respond to a target, and require 20% longer to fill a pegboard. In the biomarker continuum model of the National Research Council (Committee on Biological Markers, 1987), these effects correspond to "altered structure or function" but not "clinical disease." They would not necessarily be evident to the casual observer and would likely go undetected unless one were looking with the right assessment tools. Moreover, they typically represent more or less of a behavior that is normally present. They do not stand out as qualitative deviations in the way that a tumor deviates from normal tissue structure. Rall mused whether exposure to thalidomide would ever have been identified as a reproductive hazard if it had caused a 10-point reduction in children's IQ scores rather than limb-reduction defects (cited in Weiss, 1983). Finally,

☆ This work is based on a presentation given at the workshop "An Ecosystem Approach to the Health Effects of Mercury in the Great Lakes Basin", hosted by the International Joint Commission and The Great Lakes Commission, Windsor, Ontario, Canada, 26–27 February 2003.

* Fax: 617-730-0618.
E-mail address: david.bellinger@tch.harvard.edu.

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given that such quantitative deviations in neurobehavior are influenced by many biological, psychological, and sociological factors, achieving confidence that one has successfully isolated the portion of variance that is uniquely attributable to a neurotoxicant exposure is a formidable challenge.

The two studies generally cited as providing the strongest evidence of an adverse effect of low-dose prenatal methylmercury exposure illustrate the problem facing the risk assessor who is pondering how much weight to give subtle neurobehavioral deficits. In the Faroe Islands study, a doubling of the cord blood mercury level was associated with significantly worse performance on many neurobehavioral tests, but the largest deficit represented only about 0.16 standard deviations (the equivalent of 2.5 points on the scale used to measure IQ) (Grandjean et al., 1999). The effect sizes were larger in the New Zealand study, but the differences in scores across exposure strata were still less than 0.5 standard deviations for all major endpoints (Kjellstrom et al., 1989). Do these neurobehavioral deficits in children with greater prenatal methylmercury exposure represent an important public health problem? This line of questioning is not unique to methylmercury. Similar issues arise regarding environmental lead and polychlorinated biphenyl (PCB) exposures.

2. The clinical perspective

An observer adopting a strictly clinical perspective might conclude that the goal of a regulatory standard for an environmental chemical should be to prevent impairments that bring children to medical attention because they meet diagnostic criteria for a "disease." A small exposure-associated decrement on a continuously distributed neurobehavioral test score would therefore be considered unimportant because, even among the children with higher environmental exposures, function generally remains "within normal limits" and minor variations within the range of normal function carry relatively little import, at least in terms of a child's use of health care resources. This perspective mandates, therefore, that categorical diagnoses or clinical entities (e.g., autism, learning disability, attention deficit hyperactivity disorder, mental retardation) be used in risk assessments in which neurobehavioral toxicities are the critical health endpoints.

In opposing this clinical perspective, some argue that the instruments used to assess neurobehavioral function are so "noisy," crude, and indirect as measures of brain function that a chemical's impact must be fairly robust to affect a child's performance on them. These tests are therefore likely to underestimate the scope and severity of a chemical's true neurobehavioral toxicity, that is, to reflect only the "tip of the iceberg." From this standpoint, any exposure-related decrement in a test score that is statistically significant should be considered worrisome. Crosby et al. (2003) refer to such indices as distribution-based approaches to measuring "meaningful" differences and contrast them with "anchor-based" or "criterion-referenced" indices, which are explicitly linked to diagnostic criteria. A limitation of most distribution-based indices, however, is that they do not accord any weight to the magnitude of the performance change associated with exposure, effectively making sample size the critical determinant of whether or not a particular neurotoxicity study is interpreted as demonstrating an association. After all, even an infinitesimal difference in group means or deviation of a slope from 0, whether due to a very small true effect or entirely to the inevitable random error with which measurements are made, will be statistically significant if the sample size is sufficiently large. Therefore, unless additional efforts are taken to place the observed exposure-related difference in performance into a context that aids interpretation of its importance, this perspective does not provide a useful foundation for risk assessment. One strategy that could help in this regard would be to express the exposure-related difference in a metric-free form (e.g., correlation coefficient, standardized regression coefficient) so that its apparent impact on child outcome could be readily compared to the impacts of other factors, such as socioeconomic status, parental IQ, and birth order.

The remainder of this paper examines five issues that are relevant to evaluating the appropriateness of the clinical perspective in estimating the public health importance of the neurobehavioral toxicities associated with chemical exposures. The issues are diverse in focus and by no means mutually exclusive. The first is a purely logistical consideration, namely the fact that relying solely on clinical diagnoses as the critical health outcomes requires sample sizes that are generally not feasible. The second explores the implications of the fact that neurobehavioral nosology is fluid and that not all adverse effects are likely to be associated with discrete diagnostic labels. The third consideration involves the fact that most neurobehavioral deficits, although not themselves sufficient to diagnose a disease, can be surrogates or prodromes for clinically significant dysfunctions. The fourth and fifth issues form the heart of the effort to reconcile clinical and epidemiological perspectives on neurobehavioral toxicity. In brief, the fourth focuses on the contrast between individual relative risk and population-attributable risk and the fact that most cases of disease occur among the large proportion of the population at relatively low risk. The fifth focuses on the relationship between a small change in the central tendency of a distribution and the accompanying changes that occur in the tails of the distribution.

3. Study power is reduced when diagnoses rather than continuously distributed scores serve as the critical endpoints

On statistical grounds alone, relying on diagnoses as critical endpoints could lead to the erroneous conclusion that certain levels of exposure to a chemical are harmless when, in fact, they are associated with considerable neurobehavioral morbidity. This would represent a Type II error of inference and result in exposure standards that are insufficiently protective. Because many diseases are relatively uncommon, the likelihood of detecting a significant association between an exposure and an increased prevalence of individuals with a particular diagnosis, using sample sizes typical of environmental epidemiology studies, is low. For example, if one assumes a Type I error rate (i.e., α) of 0.05, a statistical power of 80%, and a 2% prevalence of the diagnosis in an unexposed group (the background prevalence, using the usual ± 2 SD clinical guideline), more than 42,000 subjects would be needed to detect a relative risk of 1.2 (i.e., 20% increased risk) in the exposed group (21,085 in each group); almost 8000 (3821 per group) to detect a relative risk of 1.5; and more than 2000 (1140 per group) to detect a relative risk of 2.0 (i.e., a doubling of risk in the exposed group). No epidemiological studies of low-level lead, methylmercury, or PCB neurotoxicity have approached these sample sizes. For a given sample size, therefore, diagnoses have a lower sensitivity as indices of adverse effect than do neurobehavioral tests that yield continuously distributed scores. This is readily illustrated using lead poisoning. If the screening guideline for lead were to be based on evidence of an increased prevalence of a clinically defined condition (e.g., mental retardation, seizure disorder), only childhood blood lead levels of 50–60 μg/dL (five- to sixfold greater than the current screening guideline) would be considered neurotoxic. This would represent a return to the view abandoned by the public health and pediatric communities in the 1960s, a view one that would result in no attention for many children with lead levels that would place them at increased neurodevelopmental risk. Of course, this, in itself, is not a compelling argument for using small differences in neurobehavioral test scores as the critical endpoints for risk assessment. It still leaves the question of why we should care about such "small," subdiagnostic effects. The next issue to be discussed begins to broach this issue, which is addressed more fully in Sections 5–7.

4. Because nosology (the classification and naming of diseases) is dynamic, relying solely on diagnoses as critical endpoints might lead to false-negative errors of inference

Rather than being etiologically based, many diagnoses in pediatric neurology, psychiatry, and neuropsychology are phenomenological or syndromal. That is, they are made on the basis of observable signs and symptoms and lack confirmatory laboratory findings that identify a causative factor, such as the antibody for HIV or a chromosomal anomaly. Such diagnoses are essentially a system of verbal shorthand for referring to the most commonly observed symptom complexes. They facilitate communication between professionals, obviating the need to describe *in toto* a child's presenting signs and symptoms. Providing something with a name is a powerful psychological act, however (Whorf, 1956), and imbuing such linguistic conveniences with too much significance can become dangerous if we allow them to constrain the ways in which we observe and integrate the signs and symptoms (e.g., Kushner et al., 2003; de Crespigny, 2003). Frequently, such syndromal diagnoses are assigned when an individual's score on some continuously distributed characteristic exceeds (or falls short of) some value. Although necessary for allocating treatment resources, it is not quite correct to say that one individual "has" the disease, while the individual with a score just below (or above) the cut-off does not. Rather than asking, "Does this person have it?" it is more appropriate to ask, "How much of it do they have?" (Rose, 1993). An individual classified as a case simply has more of it (but in some cases perhaps not much more) than an individual classified as being within normal limits. Van den Oord et al. (2003) demonstrated that the distributions of characteristics underlying childhood disorders such as depression and delinquency are normally distributed and not bimodal, as would be expected if the population consists of two distinct subgroups, the "normal" and the "abnormal." The same observation has been made with regard to dyslexia and reading disability (Shaywitz et al., 1992). Similarly, patients who carry a diagnosis of unipolar major depressive disorder but who have only subthreshold depressive symptoms are, nevertheless, not in remission. The presence of such symptoms is associated with increased psychosocial disability, more rapid relapse, and a poorer long-term prognosis (Judd, 2002). Although clinicians classify individuals categorically (i.e., as diseased or not diseased) based on whether discrete cut-off values are exceeded, they nevertheless rely on continuous measurements to track a patient's improvement after the initiation of treatment (e.g., the degree of glycemic control in a patient with diabetes).

An important characteristic of a nosology that includes syndromal diagnoses is that it is dynamic, as diagnostic criteria for syndromal conditions change over time as experience accrues with the symptom complex. For some disorders, this takes the form of "splitting," so that what was previously thought to represent a single condition is resolved into a family of related but distinct conditions. Such partitioning is commonplace throughout medicine, illustrated most strikingly by the practice

of attaching the prefix "non" to create labels for newly recognized clinical entities (e.g., non-insulin-dependent diabetes mellitus, non-A non-B hepatitis, non-Hodgkin's lymphoma) (Ellman and Feinstein, 1993). Two neurobehavioral disorders that have been partitioned in this way are autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). In the latest revision of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994), five subtypes of ASD are recognized (autistic disorder, Asperger syndrome, childhood disintegrative disorder, Rett syndrome, and pervasive developmental disorder not otherwise specified). Three subtypes of ADHD are currently recognized (inattentive, hyperactive, and combined). This partitioning process continues, with current debate focusing on whether both the inattentive subtype (Barkley, 2003) and ADHD that is comorbid with oppositional defiant/conduct disorder (Banaschewski et al., 2003) should perhaps be considered distinct disorders rather than ADHD variants. Absent the emergence of new disease processes or advances in the understanding of disease pathogenesis, this process reflects a change in the way the clinicians sort and classify patients' signs and symptoms rather than a change in the signs and symptoms themselves.

The evolution in nosology can also involve "lumping." Syndromal diseases that were formerly considered unrelated are recognized as variants on a single theme when a pathogenic process that links them all is discerned. An example is the 22q11 microdeletion syndrome, first identified in the mid 1990s (Glover, 1995). In a true case of the fabled blind men and the elephant, children with this syndrome, which involves considerable phenotypic variability, were formerly identified as cases of Shprintzen syndrome, DiGeorge syndrome, velocardiofacial syndrome, or conotruncal face anomaly syndrome. Which diagnosis was assigned largely depended on whether a child was seen by an endocrinologist, an immunologist, a cardiologist, or a dysmorphologist.

The fluidity of nosology is relevant to risk assessment because a neurotoxicant might cause a pattern of signs and symptoms that clinicians have not reified as a formal diagnosis by assigning it a consensus label. As noted, the neurobehavioral effects of chemical exposures generally differ quantitatively rather than qualitatively from normal function. One implication of this is that exposure to a neurotoxicant is unlikely to produce a unique "signature injury" in the way that vinyl chloride produces a deviation from normal cell morphology, angiosarcoma of the liver, that is rarely seen in the absence of this exposure. Even if an exposure were to produce a unique pattern of neurobehavioral deficits, however, the more infrequent the exposure is, the less likely it is that that pattern will be assigned a name and will enter the clinical lexicon as a new diagnosis. Nevertheless, a symptom complex that lacks a name can be just as burdensome to a child and family as one for which a label is available. Characterizing the approach that reifies diagnoses as Platonic, Goldberg (2000) cautioned against interpreting such classifications too literally, saying that "rather than carving nature at the joints, we appear to be drawing lines in the fog" (p. 9).

It should be noted that continuously distributed measures of neurobehavior are subject to the same forces that result in changes in diagnostic practices. Revised tests often add or delete subtests, offer new algorithms for deriving composite scores from subtest scores, and provide new normative data. This poses challenges for attempts to compare the results of studies that used different versions of a test, challenges that are similar to those encountered in trying to identify a secular trend in the prevalence of a disease over a period during which the case definition has evolved (e.g., autism, ADHD).

5. Reduced performance on a neurobehavioral test can be a proxy for a clinically significant impairment

A performance deficit on a neuropsychological test typically takes the form of reduced function in a specific isolated skill, such as remembering strings of digits, providing the names of objects depicted in line drawings, or reproducing abstract designs using colored blocks. How well a child performs these tasks might seem to indicate little about the child's ability to function in the "real world." In contrast, diagnostic criteria tend to be stated in terms of an inability to fulfill the expectations for behavior in specific settings or relationships, focusing on deficits that are large enough to result in "harmful dysfunctions" (Wakefield, 1997). For instance, the criteria for ADHD include the requirement that "some impairment from the symptoms is present in two or more settings (e.g., at school and at home)" and that "there must be clear evidence of clinically significant impairment in social, academic, or occupational functioning" (APA, 1994, p. 84). The diagnosis of autistic disorder requires "qualitative impairment" in social interaction and communication (APA, 1994, p. 70). To have a reading disorder, a child must present with impairment that "significantly interferes with academic achievement or activities of daily living that require reading skills" (APA, 1994, p. 50).

Although a deficit on a neurobehavioral test is unlikely to represent a harmful dysfunction that brings a child to clinical attention, it can, nevertheless, be a surrogate for such a deficit or a prodrome, a sign that a child is in the early stages of developing a harmful dysfunction. Consider the relationship between

handwriting and the ability to insert pegs in a board, a task commonly included in neurobehavioral assessment batteries. Many school assignments require children to compose narratives. To do this well requires the integration of diverse skills, including conceptualization of the theme, development of a sequence of sentences that convey it, and production of the letters that comprise the words. A child for whom the last skill, the physical act of writing, is difficult and effortful will be able to devote relatively fewer cognitive resources to theme development and composition, placing him or her at a disadvantage in carrying out this type of assignment. Despite the increasing use of word processing even among children of primary school age, handwriting continues to be a skill of considerable importance for a child's success in the school setting. Assessing it is difficult, however. Collecting a writing sample requires at least 15 min and often considerably more; coding a writing sample in ways that capture, in quantitative terms, the nature and severity of any deficiencies in penmanship might require an hour or more. Coders must learn the criteria, become demonstrably proficient in their application, and maintain proficiency over time.

In contrast to a writing sample, a pegboard is simple to administer and to score. On the grooved pegboard, for example, a child must insert 25 pegs, each of which, examined in cross-section, has a knob protruding from its surface. A hole in the board can only be filled with a peg rotated so that its orientation matches that of the hole. This task takes approximately 90 s to administer, requiring little training on the part of the examiner, and a child's score (time to complete) is objective and available immediately. In a follow-up study of 8-year-old children with a congenital heart defect, a writing sample was obtained and the grooved pegboard administered (Bellinger et al., 2003a). The time needed to complete the pegboard was highly correlated with several aspects of handwriting skill. Fig. 1 shows the letter formation, size, and alignment and spacing scores, derived on the basis of labor-intensive analyses of writing samples, for children stratified into quartiles based on time to complete the pegboard. For each dimension, a significant inverse association is evident, suggesting that a child's performance on the grooved pegboard provides, in an extremely efficient manner, a considerable amount of information about his or her handwriting skill.

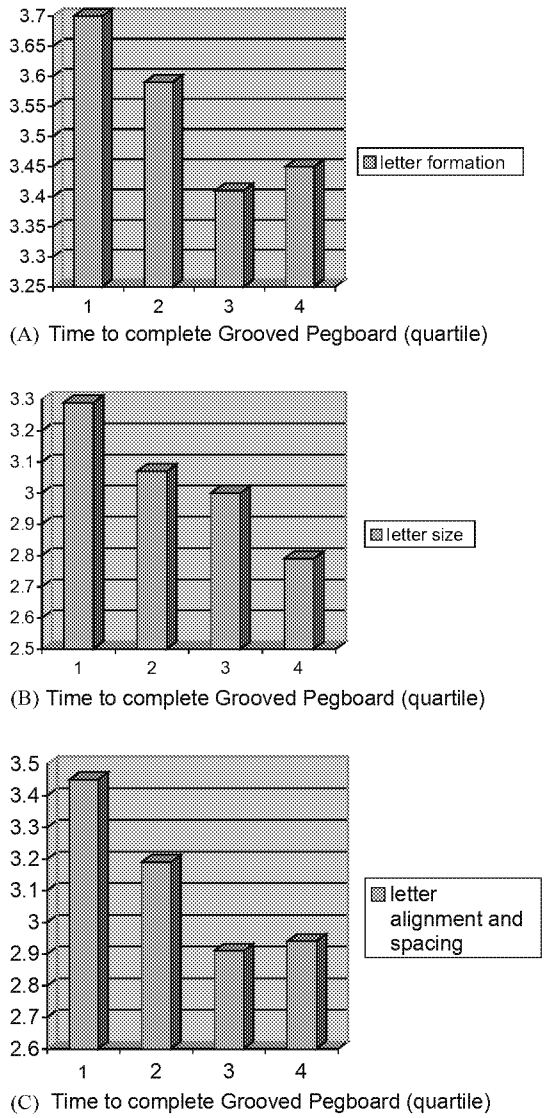

Fig. 1. Ratings of letter formation (A), size (B), and alignment and spacing (C) for 8-year-old children with D-transposition of the great arteries, a congenital heart defect, classified by time (quartile) to complete the grooved pegboard. The coding system of Johnson and Carlisle (1996) was used to score handwriting samples on these dimensions. Children who were slower to complete the pegboard were assigned significantly lower scores on each aspect of handwriting (letter formation, $P = 0.0001$, Pearson correlation coefficient = 0.42; letter size, $P = 0.029$, Pearson correlation coefficient = 0.28; letter alignment and spacing, $P = 0.002$, Pearson correlation coefficient = 0.36), indicating that this brief, objective test conveys considerable information about a skill that contributes to a child's success in school.

Children's visual–motor integration skills are frequently assessed using design-copying tasks, an example of which is the Rey–Osterrieth complex figure (ROCF) (Fig. 2). The child is provided with a blank sheet of paper and a marker and instructed to copy the model, which remains in full sight. The ROCF was administered to the same sample of children from whom handwriting samples were collected. ROCF copies were blindly classified into five categories based on overall goodness of organization and style, as shown in Fig. 3 (Bellinger et al., 2003b). The ability to produce a good copy varied greatly among children, but one might ask, "So what?" Because copying figures is not a skill that is explicitly called upon in a child's natural settings, a deficit in the ability to do so would not seem to be a harmful dysfunction. ROCF category, however, was associated, in a monotonic manner, with the percentage of children receiving remedial services in school

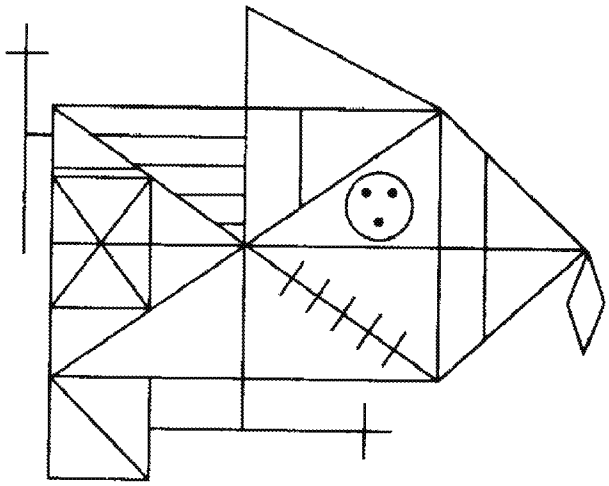

Fig. 2. The Rey–Osterrieth complex figure (ROCF). In the standard administration of the ROCF, a child is instructed to reproduce this figure. The figure remains on the table in the child's view. There is no time limit. Reproduced by special permission of the Publisher, Psychological Assessment Resources, Inc., 16204 North Florida Avenue, Lutz, Florida 33549, from the Rey Complex Figure Test and Recognition Trial by John E. Meyers, PsyD, and Kelly R. Meyers, BA. Copyright 1992 by PAR, Inc. Further reproduction is prohibited without permission of PAR, Inc.

($P = 0.05$) (Fig. 4). Fewer than 10% of children with the best ROCF performance (category 5) required such academic supports versus more than 50% of children with the worst performance (category 1). A child's performance on the ROCF appears to provide information germane to the criteria applied to making the resource allocation and treatment decisions attendant to learning disability, which represents a clearly harmful dysfunction for the child and a substantial cost to society.

One might reasonably ask, "Why not simply use need for remedial academic services as the study endpoint" rather than something that is as tedious to score as the ROCF? Typically, an investigator is interested not only in establishing the final outcome, such as failure to make adequate progress in school, but also in discerning the reasons for the child's failure. What is it that impedes progress? It is by examining the patterns in a child's scores on tests such as the ROCF that such questions can be answered.

6. Population risk is not the same as individual risk; in absolute numbers, more cases of disease arise among individuals with values of a risk factor that fall in the middle of the distribution than among individuals with values that fall in the extreme tails of the distribution; therefore, shifting the entire distribution toward "healthier" values can be an effective strategy for reducing the total disease burden in a population

In assessing the public health importance of an environmental exposure, it is critical to take account

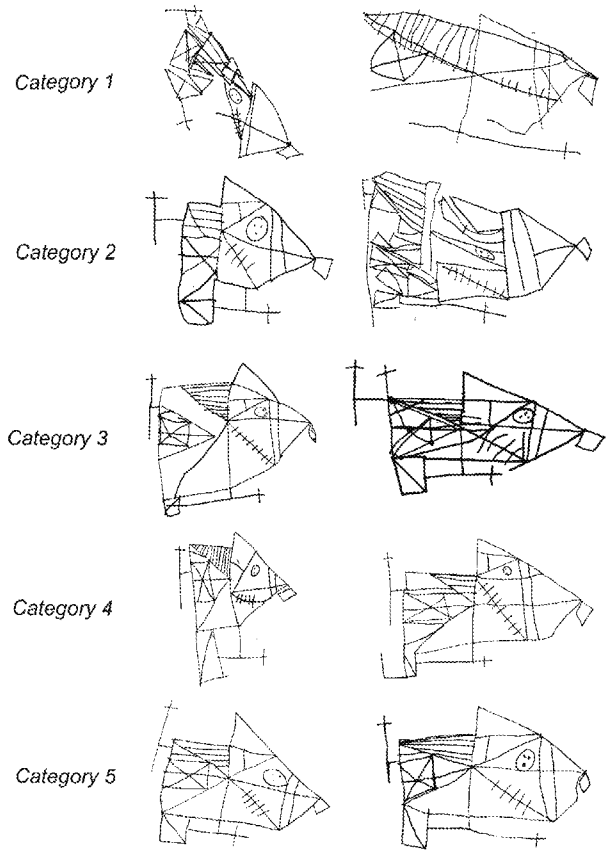

Fig. 3. Examples of Rey–Osterrieth Complex Figure copies scored at 5 levels based on overall goodness of organization and style in a cohort of 8-year-old children with a congenital heart defect (D-transposition of the great arteries). Reprinted by permission of Lippincott Williams & Wilkins. From Bellinger, D.C., Bernstein, J.H., Kirkwood, M.W., Rappaport, L.A., Newburger, J.W. 2003. Visual–spatial skills in children following open-heart surgery. J. Dev. Behav. Pediatr. 24, 169–179.

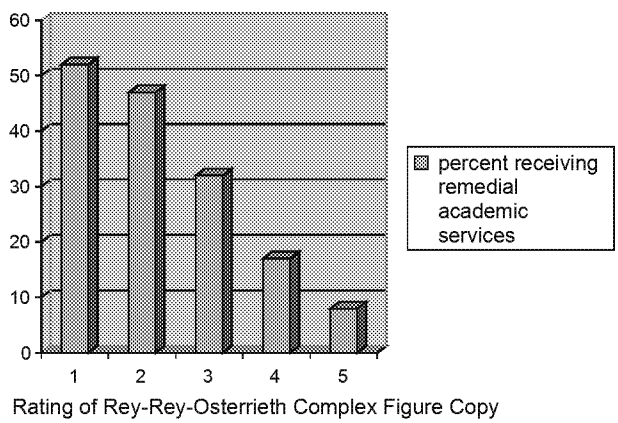

Fig. 4. The proportions of children at each of the 5 levels of overall goodness of organization and style of the Rey–Osterrieth complex figure copy who were receiving remedial academic services in school ($P = 0.05$). Although the "real world" importance of poor design copying might not be readily apparent, children with such impairment are at increased risk of failing to achieve adequate progress in school.

of the distinction between individual risk and population risk. Individual risk is often expressed in terms of relative risk, the increase or decrease in the likelihood that someone will become a case given a particular characteristic (e.g., age, gender, exposure status). Population risk is often expressed in terms of attributable risk, the proportion of cases in a population that are due to the risk factor of interest. An important difference between individual relative risk and attributable risk can be illustrated using the Framingham Study data (Rose, 1981). Fig. 5 shows that an individual's risk of dying from coronary heart disease (CHD) is strongly associated with serum cholesterol level. Someone with a level of 340 mg/dL is clearly at much greater risk than is someone with a level below 200 mg/dL. The histogram in Fig. 6 shows the prevalence, in the Framingham Study population, of different serum cholesterol levels. Fortunately, very high levels, at which individual risk is greatly increased, are relatively uncommon. Attributable risk, however, is the product, across exposure strata, of relative risk and prevalence. Table 1 shows the excess CHD deaths attributable to cholesterol within the strata defined by serum cholesterol level. Of the total of 34 excess deaths predicted per 1000 people over a 10-year period (at the time the study was conducted), the great majority would be expected to occur among individuals with cholesterol levels in the middle portion of the serum cholesterol distribution. It is not surprising, therefore, that the frequency distributions of serum cholesterol levels look very similar for those who developed CHD and those who did not (Fig. 7) (Rose, 1985). Clearly, one will be wrong most of the time in trying to predict the *specific*

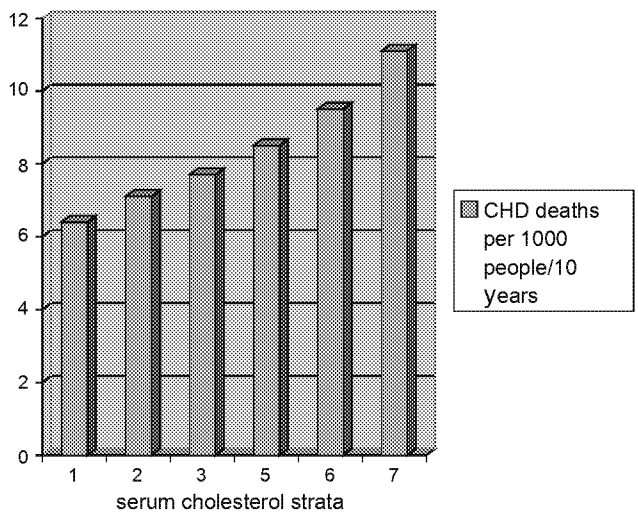

Fig. 5. Data from the Framingham Study showing the association between serum cholesterol level and coronary heart disease (CHD) death rate. Serum cholesterol levels (mg/dL) defining the strata are: <190, 190–220, 220–250, 250–280, 280–310, >310. Death rate increases monotonically across serum cholesterol strata. From data in Rose (1981).

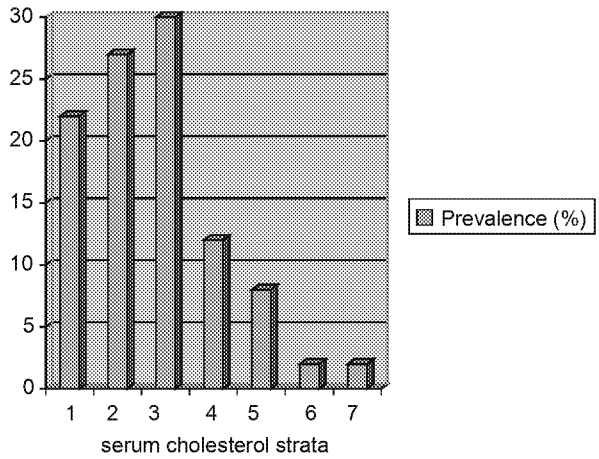

Fig. 6. Data from the Framingham Heart Study on the prevalence in the study sample of individuals with serum cholesterol levels in different ranges (adapted from Rose, 1981). Serum cholesterol levels (mg/dL) defining the strata are: <190, 190–220, 220–250, 250–280, 280–310, 310–340, and >340. Serum cholesterol levels above 310 mg/dL are relatively infrequent.

individuals in a population who will die from CHD based on serum cholesterol level, although one will generally be more successful in predicting that, given two randomly selected individuals, the one with the higher serum cholesterol is more likely to die from CHD. This is the logic behind successful clinical-risk stratification models (e.g., Pocock et al., 2001).

The contrast between population and individual risk is also illustrated by considering the way in which the risk and incidence of Down syndrome (DS) change as a function of maternal age (Table 2). The incidence of DS per 1000 births is approximately 50 times greater among women older than age 44 years than among women less than 30 years of age (34.6 versus 0.7). Because population-attributable risk is calculated by summing the products of relative risk at a particular maternal age stratum and the fecundity of women in that stratum, more than half (51%) of DS cases occur among women less than 30 years of age and only a small percentage (2%) among women older than 44 years of age. The clinician, quite rightly, focuses on the incidence rate of 34.6/1000 among older women insofar as this is clearly the number of greatest import for deciding how to manage the pregnancy of the 45-year-old patient in the waiting room. In contrast, the epidemiologist trying to identify ways to reduce the prevalence of DS in the population will focus, again quite rightly, on the 51% of cases that occur among women younger than 30 years of age.

These observations lead to several principles that might appear to be somewhat counterintuitive from the standpoint of clinical reasoning. First, "a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk" (Rose, 1985, p. 431). Second, a preventive measure that

Table 1
Prevalence of serum cholesterol levels, mortality rates for cholesterol-associated coronary heart disease (CHD), and excess deaths from cholesterol-associated CHD

Serum cholesterol (mg/dL)	Prevalence (% of population)	Deaths from CHD per 1000 population/10 years	Excess deaths from CHD, per 1000 population/10 years, attributable to cholesterol	Percentage of excess CHD deaths
< 190	22	6.4	Reference group	—
190–220	27	7.1	5	14.7
220–250	30	7.7	11	32.4
250–280	12	8.5	8	23.5
280–310	8	9.5	7	20.6
>310	4	11.1	3	8.8
			Total excess deaths = 34	100

Adapted from Rose (1981, Fig. 3).

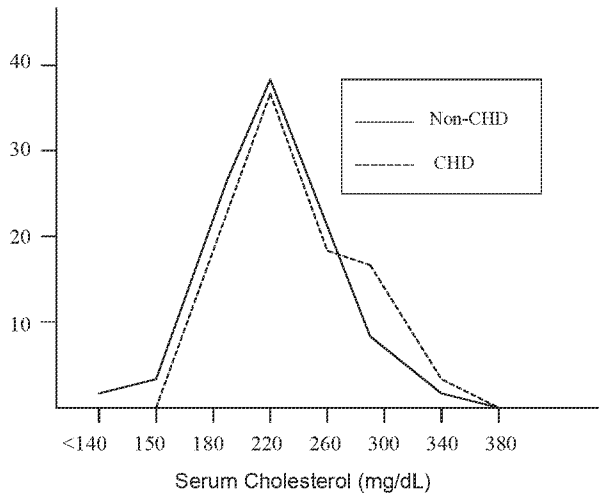

Fig. 7. Frequency distributions of the serum cholesterol levels of men (50–62 years old) in the Framingham Heart Study who developed coronary heart disease (CHD) and of individuals who did not (Rose, 1985; original data from Kannel et al., 1971). An elevated serum cholesterol level is a strong individual risk factor for CHD, but because the number of excess deaths within a particular cholesterol stratum is the product of the relative risk associated with levels in that stratum and the number of individuals in that stratum, most cases of CHD will occur among individuals with levels in the middle portion of the distribution. Thus, the cumulative frequency distributions of cholesterol levels among cases and noncases are similar in terms of mean and standard deviation.

brings much benefit to the population might offer little benefit to each individual in the population (the "prevention paradox")(Rose, 1985). Of course, the latter principle provides the foundation for many public health interventions, such as immunizations against infectious childhood diseases and the use of seatbelts, that prevent diseases or events that are relatively rare but which, for an affected individual, can cause considerable morbidity. Third, the causes of disease incidence in a population can appear to differ from the causes of disease incidence in individuals. This seemingly nonsensical statement can be illustrated by the following hypothetical example. Suppose that 100% of the people in population A smoke cigarettes and the prevalence of lung cancer is 33% (i.e., approximately one-third of smokers get lung cancer). Smoking clearly could not explain why one individual in the population becomes a lung cancer case while another individual does not. The risk factors identified by epidemiologic studies would likely involve genetic susceptibility or coexposures (e.g., diet, air pollution). Suppose that in population B, the prevalence of smoking is 9%, that no nonsmokers develop lung cancer, and, as in Population A, one-third of smokers develop lung cancer, resulting in a lung cancer prevalence of 3%. Smoking would be identified as a strong risk factor for lung cancer in this population, and the risk factors identified in Population A would probably be identified as risk modifiers in Population B. Clearly, the 11-fold difference between populations in the prevalence of smoking accounts for most of the difference between populations in the incidence of lung cancer (assuming that the distributions of genetic susceptibility and relevant coexposures are comparable in the two populations). In part, the issue is the contrast between *the* cause of lung cancer, in a mechanistic sense, and *a* cause of lung cancer (Doll, 2002). *The* cause, the critical pathogenetic process, is very likely to be the same among individuals in Populations A and B. Differences in the distributions of the critical risk factors will, however, lead to different factors being identified as the major predictors of disease in the two populations.

One form in which the confusion between individual risk and population risk is expressed is the argument that the effect sizes reported in neurobehavioral toxicity studies are trivial because they are generally smaller than the standard errors of measurement (SE_M) of the tests used. Because this claim seems, at first blush, to be reasonable, it warrants examination. The SE_M is an estimate of the measurement error in a child's observed score on a test. Inversely related to the reliability coefficient of the test, it is used to define the range within which a child's true score is likely to fall (i.e., the 95% confidence interval is observed score $\pm 1.96\ SE_M$). For example, the SE_M of the WISC-III full-scale IQ for a 9-year-old child is 3.35 points. If the child's tested IQ is

Table 2
Risk and incidence of Down syndrome (DS), stratified by maternal age

Maternal age (years)	Risk of DS (per 1000 births)	Percentage of births in age group (% of total births)	Percentage of total DS births occurring in age group
<30	0.7	78	51
30–34	1.3	16	20
35–39	3.7	5	16
40–44	13.1	0.95	11
>44	34.6	0.05	2

Adapted from Alberman and Berry (1979).

100, one can therefore be 95% confident that the child's true IQ is between 93.4 and 106.6.

Does an appeal to the SE_M provide a sound basis for concluding that, for example, a statistically significant 3-point deficit in the mean IQ of an exposed group, compared to an unexposed group, is trivial because it is "in the noise?" One would have to assume that the true mean scores are equivalent in the exposed and unexposed groups but that, by chance, the measured IQs of children in the exposed group are *systematically* underestimated (i.e., the children's true scores fall in the upper region of the confidence intervals around the children's observed scores) and that the measured IQs of children in the unexposed group are *systematically* overestimated (i.e., the true scores fall in the lower region of the confidence intervals around the children's observed scores). That the direction of measurement error would be sufficiently correlated with exposure status to produce this result seems highly unlikely (more specifically, the probability would be <0.05). The SE_M is a statistical concept important for interpreting an individual's scores, but it is misleading to invoke it to draw inferences about the clinical significance of a difference between group means. This latter task demands a different level of analysis, one that focuses on population risk rather than on individual risk.

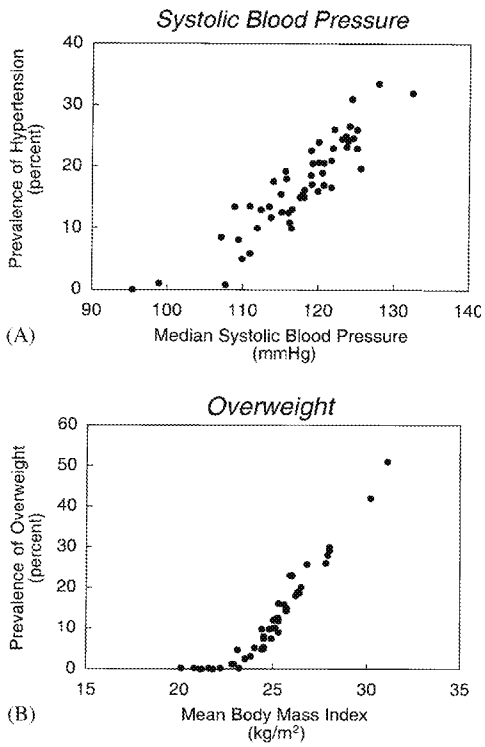

Fig. 8. Scatterplots for the 52 populations contributing data to the Intersalt study of (A) the median systolic blood pressure within a population and the prevalence of hypertension in that same population and (B) the mean body mass index in a population and the prevalence of obesity in that same population (Intersalt Cooperative Research Group, 1988). These relationships indicate that the central tendency in a population on the continuously distributed characteristic underlying a diagnosis is strongly associated with the prevalence of individuals within the population with values that are sufficiently extreme to warrant assignment of the diagnosis.

7. Because a population distribution moves as a whole, a small change in the mean signals predictable accompanying changes in the tails of the distribution, where individuals who meet diagnostic criteria are found

A decrement in the mean value of a health indicator in a sample of exposed individuals implies an accompanying shift in the proportion of individuals in the source population who meet diagnostic criteria for the clinical entity corresponding to the indicator. In other words, a shift in group mean is not important because of what it indicates about the average change among members of the study sample, but instead because of what it implies about the changes in the tails of the distribution in the population from which the study sample was drawn.

This can be appreciated by examining the association between the central tendency of the distribution of a health indicator and the proportion of individuals with values of the indicator that exceed the clinical cut-off used to sort people into patients and not patients (Rose and Day, 1990). Fig. 8 shows two scatterplots involving 52 populations from around the world: (A) the median systolic blood pressure in a population and the prevalence of hypertension in the same population and (B) the mean body mass index in a population and the

prevalence of obesity in the same population (Intersalt Cooperative Research Group, 1988). The correlations are clearly very high. Moreover, for both characteristics, the slopes are fairly steep, indicating that, in comparing two populations, a small difference between the population means for the health indicator is associated with a surprisingly large difference in the prevalences of clinical cases in the two populations. Similar relationships hold between the mean alcohol intake in a population and the prevalence in the population of alcoholism and between mean sodium intake and the prevalence of high sodium intake. The mean value of a population distribution is thus highly informative about the proportion of individuals in the population who have deviant values.

An important characteristic of the distribution of a health indicator is thus that it moves up and down as a whole, such that a change in the mean value produces a predictable change in the prevalence of clinically defined cases in the source population. For example, based on the scatterplot of mean systolic blood pressure and the prevalence of hypertension in the 52 populations represented in Fig. 8, one can predict that a reduction of 1 mmHg in mean systolic blood pressure will be associated with a reduction of 1% in the prevalence of hypertension. Therefore, if the prevalence were 15%, a 5-mm reduction in mean systolic blood pressure, a reduction that is insignificant for an individual (perhaps even within the SE_M for the measurement of blood pressure), would result in a hypertension prevalence of 10%, or a decline of 33%. On this basis, Rose (1981) estimated that a population strategy consisting of an intervention that reduced the mean blood pressure in a population by as little as 2–3 mmHg would be as effective in reducing the prevalence of hypertension in that population as a high-risk strategy consisting of drug therapy for all individuals with clinically defined hypertension. Along the same lines, a 2-kg decrease in the mean body weight of individuals within a population would result in a halving of the prevalence of individuals with clinically defined obesity (Rose, 1991).

Rose's predictions were based solely on cross-sample comparisons. They have been validated, however, by means of the longitudinal measurement of secular trends in the relationship between group mean and the prevalence of deviant cases within the same population. In a 7-year follow-up of a sample drawn from the general population, the change over time in the prevalence of individuals meeting criteria for a psychiatric disorder was linearly related to the change over the same period in the mean number of psychiatric symptoms reported among members of the population (Whittington and Huppert, 1996). Similarly, in the German Cardiovascular Prevention Study (Laaser et al., 2001), a multisite intervention trial to reduce the prevalence of risk factors for cardiovascular diseases, the decline in the proportion of cases following the intervention matched closely the decline predicted based on the change in the mean value of the risk factor.

In the realm of neurotoxicity studies, this principle has been demonstrated most clearly for lead. Several meta-analyses suggest that a doubling of childhood blood lead, for example from 10 to 20 μg/dL, is associated with a 1–3 point decline in IQ score (Schwartz, 1994; Pocock et al., 1994; International Programme on Chemical Safety, 1995), a change that is well within the SE_M of IQ tests. Reducing the mean blood lead level in the population would be unlikely to provide discernable benefit to any randomly selected child in the population, but the prevention paradox predicts that the benefit to the population would be substantial in terms of reducing the prevalence of IQ scores associated with a need for remedial academic services, reduced lifetime earning potential, etc. What is sometimes overlooked, moreover, is that if a distribution retains its shape and variance, an increase in the area of the lower tail will be accompanied by a mirror image decrease in the area of the upper tail, in this case a reduction in the prevalence of high IQ scores. This argument need not be made solely on statistical grounds, but can be illustrated using the data from two studies. Fig. 9 shows the observed cumulative frequency distributions of verbal IQ for school-aged children stratified by dentin lead level (Needleman et al., 1982). While the median verbal IQ scores of the two groups differed by fewer than 10 points, the proportion of children in the high lead group with scores below 80 was threefold higher than the proportion in the low lead group. Similarly, no child in the high lead group had a score above 125, while 5% of children in the low lead group did. Thus, the modestly lower median score in the high lead group was associated both with a large increase in the percentage of children with scores in the range of clinical concern and with a truncation of the distribution at the upper end. Fig. 10 shows the cumulative frequency distributions for residualized mental development index scores of 2-year-old children, stratified by the concentration of lead in umbilical cord blood (low: <3 μg/dL; medium: 6–7 μg/dL; high: >10 μg/dL) (Bellinger et al., 1987). The distribution rises much more rapidly for the high lead group, with the percentage of children scoring 10–20 points below expected being two to three times greater than the corresponding percentages in the mid and low lead groups.

8. A possible resolution

Neuropsychologists must do a better job of explaining the ecologic validity of the performance changes measured as outcomes in neurotoxicity studies. It would

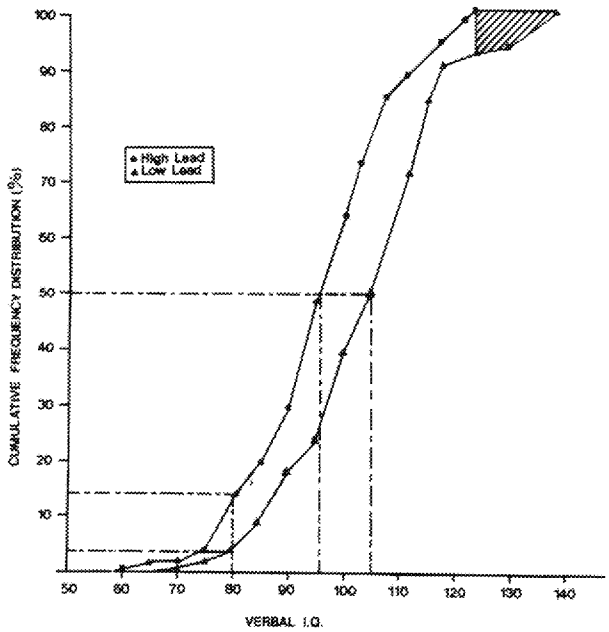

Fig. 9. Cumulative frequency distributions of verbal IQ for children with high or low dentin lead levels. The median (50th percentile) verbal IQ in each group is shown, as well as the frequency of verbal IQ scores of 80 or less (Needleman et al., 1982). Although the medians of the low and high lead groups differ only modestly, this difference between distributions in central tendency is accompanied by a threefold difference, favoring the low lead group, in the proportions of children in the two groups with verbal IQ scores below 80. Moreover, 5% of children in the low lead group had a verbal IQ greater than 125, whereas no child in the high lead group scored in this range. This is an empirical illustration of the principle that a distribution tends to move up or down as a whole, so that a small change in central tendency will be accompanied by substantial changes in the absolute numbers of individuals with values that exceed or fall short of cut-off scores used to define "disease" or "impairment." Reproduced from Needleman, H.L., Leviton, A. and Bellinger, D. (1982) Lead-associated intellectual deficit. N. Engl. J. Med. 306, 367. Copyright© 1982 Massachusetts Medical Society. All rights reserved.

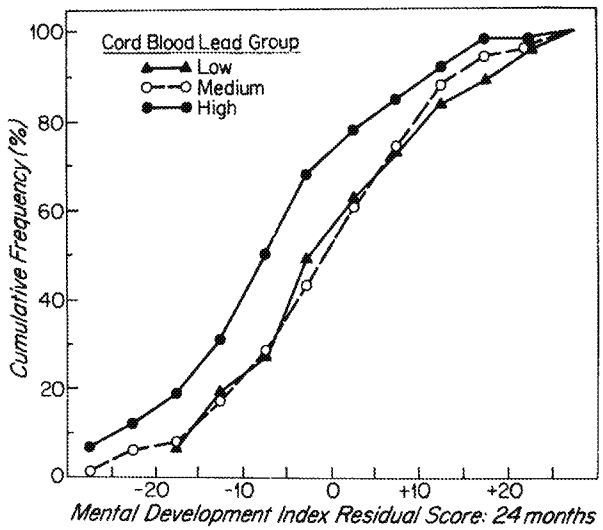

Fig. 10. Cumulative frequency distributions of adjusted (residualized) mental development index scores of children stratified by the concentration of lead in umbilical cord blood (low, $<3\,\mu g/dL$; medium, 6–7 $\mu g/dL$; high, $>10\,\mu g/dL$). Based on data from Bellinger et al. (1987).

be helpful to show how such changes are prodromic or are at least correlated with dysfunctions of obvious importance. Epidemiologists should recognize the difficulty that many have understanding the prevention paradox, in particular, the fact that most cases of disease occur in individuals with apparently benign risk factor profiles, that small changes in the central tendency of a population distribution have substantial implications for the overall burden of disease in the population, and that shifting an entire distribution toward lower risk is directly relevant to the clinician's goal of reducing morbidity. Clinicians need to look beyond the consensual, but always provisional, systems for classifying individuals according to diagnosis. Such sorting is necessary to allocate treatment resources and to obtain third-party reimbursement, but it is a system that can impede apprehension of the public health dimensions of a problem. As Rose recommended, even if someone does not meet criteria and thus have a disease, that person might "have a little of it." Whether many or few people in a population have a little of it might have minimal impact on a clinician's daily practice but still be vitally important from a public health standpoint.

The clinical and epidemiological perspectives are ultimately complementary rather than incompatible. Within the bounds established by their respective assumptions, both perspectives reveal something important about disease occurrence. The clinician, being most concerned with the tails of a distribution, is correct in saying that an individual whose function is altered by an amount equal to that by which the group mean is shifted is unlikely to meet diagnostic criteria for a disease. The epidemiologist is correct in saying that most cases of disease occur among individuals with values of the relevant risk factor that are within normal limits and, furthermore, that a small shift in the mean of a risk factor toward less optimal function implies a corresponding increase in the prevalence of clinically defined cases that would be observed empirically (i.e., that would be statistically significant) if the sample size were sufficiently large. Such a shift in the mean, therefore, is a marker of changes that, eventually, will directly impact clinicians in the form of increased numbers of people who meet diagnostic criteria. Insofar as prevention of disease, as well as its treatment, is part of the medical mandate, factors that produce small shifts in the population means on health indicators should be of great concern to clinicians. They are a sign that some members of the population who were formerly considered healthy have crossed the not-so-bright line separating normal and abnormal and now warrant the label of patient.

Acknowledgments

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Low-level lead exposure and intelligence in children

Jack R. Nation*, David H. Gleaves

Psychology Department, Texas A&M University, College Station, TX 77843-4235 USA

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Abstract

Numerous prospective and cross-sectional studies of the relation between low-level lead exposure and cognitive functioning in children have suggested that intellectual and academic performance declines as lead burdens increase. Kaufman [Arch. Clin. Neuropsychol. (2001)] raises questions regarding interpretive issues along these lines, and therein challenges the wisdom of using the available lead/IQ data complex as an essential element of the decision-making process that leads to policy statements. In this article, we address some of the concerns expressed by Kaufman, and conclude that each of his five points are logically or statistically flawed, as is his overall strategy of critiquing individual studies after methodologically sound meta-analyses have been performed. Kaufman is perhaps correct that the findings from correlational research on low lead levels and IQ loss should be interpreted with caution, but the caution extends equally if not more greatly in the direction of previous research having underestimated the relationship between the two variables in question.
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Keywords: Children; Cognition; Lead; Intelligence

> Some circumstantial evidence is very strong, as when you find a trout in the milk.
> — Henry David Thoreau (November 11, 1850)

This entry into the journal of the American naturalist was aimed at the common practice among 19th century milk suppliers who, in an effort to deceive customers and thereby increase their profits, would deliver containers with water added to the milk. The point being, of course, that on occasion, related events take on greater significance when practical considerations limit alternative explanations of the phenomenon. This would seem to be the position taken by many members of the scientific community concerned with characterizing

* Corresponding author.

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the relation between chronic exposure to low levels of lead in children and declining scores on conventional intelligence tests. The argument is that, on the whole, the data on the topic are so compelling that the only sensible conclusion is that "safe" blood lead levels must be adjusted downward. In addition, this is precisely what happened in 1991 when the Centers for Disease Control (CDC) established the current blood lead guideline of 10 μg/dl.

Sensitivity to the issue is understandable, given the enduring nature of the problem. Despite the fact that child blood lead levels were reduced significantly between 1976 and 1991 (Pirkle et al., 1994), lead contamination persists from exposure to soil (Mielke, 1999), painted surfaces (Shannon, 1996), and other environmental vectors. Indeed, in 1994 Brody et al. estimated that 1.7 million or almost 9% of children in the U.S. under the age of 6 years had blood lead levels that were equal to or exceeded 10 μg/dl (Brody et al., 1994).

As relates to matters of intellectual function, Kaufman (2000) provides a welcome opportunity to debate the issue of lead/intelligence interactions within a scholarly forum. Few systematic challenges to the reference literature in this area have been attempted, and considering the enormous financial, health, and societal impact of policy decisions regarding acceptable blood lead levels, careful and cautious review of relevant findings is in order. It is within this context, that the following comments are offered and the strength of the "circumstantial evidence" assessed.

In his examination of the literature on developmental lead exposure and loss of intelligence, Kaufman adopts the approach of evaluating 26 of the "better" studies in the area that were included in one or more of three meta-analyses (Needleman & Gatsonis, 1990; Pocock, Smith, & Baghurst, 1994; Schwartz, 1994). Each investigation is examined vis-à-vis five recognized shortcomings. We have three general concerns with Kaufman's argument, as well as more explicit concerns with each of his five points. Our first general concern is that his basic strategy of reexamining the original 26 studies in terms of "positive or negative outcomes" is misguided. The purpose of meta-analysis is to go beyond examining significant or nonsignificant results at the individual study level, and calculate effect sizes across numerous studies. In his recent article "Science and ethics in conducting, analyzing, and reporting psychological research," Rosenthal (1994) describes meta-analysis as "an ethical imperative" and describes in detail why this should be so:

> Meta-analytic procedures use more of the information in the data, thereby yielding (a) more accurate estimates of the overall magnitude of the effect or relationship being investigated, (b) more accurate estimates of the overall level of significance of the entire research domain, and (c) more useful information about the variables moderating the magnitude of the effect or relationship being investigated. (p. 130).

Along similar lines, Schmidt (1996) offers a numeric example where a series of studies are completed on a treatment with, *in reality*, a medium effect size $d = 0.5$. Because of the common problem of low power (which would be much worse if researchers had controlled for multiple comparisons as Kaufman suggests — more on this issue below), in this hypothetical example, this real effect would be found only in 37% of the studies. However, meta-analysis would correctly determine a medium effect size. This hypothetical example sounds rather like Kaufman's discussion of the literature on blood level and IQ (e.g., p. 320). Furthermore, his use of the term "negative results" is inappropriate here. This term would

imply IQ gains. All that can be said here is "not statistically significant" but, as noted above, the meta-analyses take the science beyond this practice and synthesize research to better estimate effect sizes. Thus, Kaufman's overall strategy arguably is moving science backward rather that forward.

A second general concern is that, throughout the paper, Kaufman makes statements as if they are factual when they could be more accurately described as conjectural. For example on page 322, he writes:

> ...the results [of a multiple regression analysis] for one sample are not readily generalizable to samples that differ in meaningful ways from the original sample. Therefore, the results of the Bellinger et al. (1992) study only generalize to similar samples of high SES white children, not to minorities or to whites from lower social classes.

A more correct statement is that the results may or may not be generalizable to other samples. One should not assume that the results are generalizable, but it is also erroneous to assume (as does Kaufman) that they are not generalizable. Another example of Kaufman stating something as if it were a fact is on page 323 where he writes, "only the adjusted values [from an analysis of covariance] are interpretable." As we will discuss in greater detail below, this may or may not be the case. In some circumstances (e.g., with high multicollinearity), the adjusted values from such analyses are the *least* interpretable and meaningful.

A final example of Kaufman stating with certainty what in actuality is opinion, perspective, or possibility is that:

> The *correct* [italics added] procedure is to apply a statistical correction to control for the error that occurs when many analyses are done at once. Several of the lead researchers have used this shotgun approach, but none have controlled for the known errors that accompany this approach. (p. 330)

This statement is erroneous for two reasons. First, as we will discuss later, there is not widespread agreement that the "correct" procedure when performing multiple comparisons is to adjust the alpha level. Whether or not one does this is really based on the nature of the research question being asked, and whether one wants to minimize Type I or Type II errors (see Stevens, 1996). Using a correction may minimize Type I errors, but may drastically reduce power and increase the rate of making Type II errors. It is also erroneous to refer to the "known errors" that accompany conducting multiple tests. Such a statement is based on a misunderstanding of the probability of making Type I errors (see Pollard & Richardson, 1987). Type I errors may or may not occur when multiple tests are performed; it all depends on whether or not the null is true. If the null is false (in this case that lead does cause IQ losses in children) then it is impossible to make a Type I error (i.e., to conclude that lead is harmful when it is not) no matter how many analyses one does. One could only make a Type II error, and the lower one's alpha level, the greater the probability of making a Type II error.

Our final general concern is how Kaufman treats and refers to the issue of causation. On page 313, he makes the statement that "resolving the causality issue is beyond the scope of this paper." We find this statement particularly curious when one examines the overall context of the paper. Kaufman's general thesis is about causation, and throughout the paper,

he makes numerous statements strongly implying causality. As an example, on page 311, he writes "whatever environmental variables are responsible for the steady gain are likely to lead to loss of intellectual functioning when they are diminished or withdrawn." Thus, his argument is clearly that environmental factors other than lead are "causing" IQ losses.

Although we believe that these overall, general concerns are sufficient to call into question Kaufman's conclusions, we have additional concerns with each of the five shortcomings that Kaufman points to in the original studies. Below, we address each of the five points.

1. Critique of the best-designed studies relating low BLLs to IQ loss

1.1. Shortcoming #1 — uncontrolled variables cloud conclusions drawn from even the best studies

The initial methodological concern expressed in the Kaufman paper relates to sources of uncontrolled variation. Included in the list of uncontrolled variables, is parenting skill/style. Because parental communication and participation is correlated with IQ (e.g., Fulton et al., 1987), and because IQ tends to be higher and lead levels lower when both parents are in the home (Baghurst et al., 1992; McMichael et al., 1994), the suggestion is that parental attention, involvement, etc., may represent concomitant variables that contribute substantially to observed IQ losses in lead-exposed children. Such an argument should be considered, of course, but it is unconvincing for a number of reasons, not the least of which is the fact that, as Kaufman notes on page 306, it is impossible to document the veracity of reports from parent interviews of the sort that were used in investigations such as Fulton et al. (1987). Even if the results of such parent studies could be believed, lead is not excused as a primary determinant of IQ loss, inasmuch as the toxicity profile may include disturbances in caretaking that may play a modulatory role in intellectual development. This line of reasoning obviously offers no support for the notion that lead contamination causes a drop in IQ, but neither can the pattern of results be used to minimize concerns of lead/IQ interactions.

A major problem with Kaufman's argument is how he continually writes about the need for and use of statistical methods to control for these potentially confounding variables. He writes that "technically, a confound in a lead–IQ study correlates significantly with both the dependent variable of children's IQ and with the independent variable of BLL" (p. 310). He then describes the data analytic strategy:

> ... investigators have uniformly used appropriate, sophisticated regression analysis procedures. They have identified various sets of potentially confounding or contaminating variables and have entered these variables into the regression equation in an attempt to control as much of the unwanted variability and possible. Then, lead level is added to the equation to see if it contributes a significant amount of variance to the prediction of IQ, over and above the prediction that is obtainable from the confounds alone. (p. 312)

Kaufman's definition of a confound is accurate. However, the scenario he describes is just the type of situation when statistical control is, at best, problematic, or more likely totally

inappropriate. It is the essential problem of multicollinearity, which makes interpretation of a multiple regression analysis difficult. For example, as noted by Wampold and Freund (1987):

> The high correlation among some or all of the independent variables is called multicollinearity. ... multicollinearity is undesirable for several reasons. First and most importantly, if the independent variables are highly correlated, none of them will demonstrate a substantial unique contribution to the prediction of the dependent variable... Nevertheless, it would be incorrect to conclude that [the predictors] are unimportant... A second problem of multicollinearity is that the estimates of population partial regression coefficients are highly unstable, resulting in decreased probabilities of obtaining statistically findings. (p. 378)

When used properly, statistical control techniques such as analysis of covariance or hierarchical regression can be powerful tools for the behavioral scientist. They allow the researcher to increase the precision of research by partitioning out error variance (Hinkle, Wiersma, & Jurs, 1988; Pedhazur, 1982). However, their use is most appropriate in randomized designs (e.g., Kirk, 1982). Lord (1969) noted that when subjects are not randomly assigned to treatment groups, there is no logical or statistical procedure that can properly allow for uncontrolled, preexisting differences between groups. More importantly, for a covariate (control variable) to be effective in controlling for an extraneous variable, the covariate must be linearly related to the dependent variable and *unaffected by the treatment or independent variables* (Hinkle et al., 1988; Porter & Raudenbush, 1987), or precisely opposite the situation described by Kaufman. If a covariate is significantly correlated with both the dependent variable(s) and the independent variables, then the results of the analysis may be highly misleading and, at times, meaningless (Pedhazur, 1982). The analysis will simply partial out not just variance attributable to the covariate, but also variance shared by the covariate and the independent variable.

Thus, when you have this situation (high correlations between lead levels and the various confounds), while you are "controlling" for [partialling out] the effects of the confounding variables, you are also partialling out [removing] the effects for lead. The more highly correlated are lead and the confounds, the more of the variance directly attributable to lead is removed. Overall, you get an underestimate of the actual effect of lead and the results are less likely to be statistically significant. Thus, Kaufman's statement that "A more correct statement is that any significant increase in prediction is due not only to lead level, but also to all other potentially important variables, known or unknown, that were not controlled in the study" (p.312) is not justifiable. A better statement is that although the actual effects of lead on IQ *may* be lower than those obtained because of uncontrolled variables, the actual effects also may be *higher* because of the overlap in predictor variables and statistical techniques having partialled out the effects of lead.

In conclusion, it is likely that there are uncontrolled sources of variation in human lead studies of IQ loss. However, it is just as likely that the use of statistical control has controlled for not only additional sources of variance but also for the effects of lead, thus leading to underestimates of the actual effect sizes. Furthermore, when a converging body of data points to a common underlying variable as a responsible agent in cognitive and intellectual dysfunction, caution must be exercised in minimizing such a causal variable. Diverting

attention to other possible sources of negative influence in no way alters the need to attend to a primary risk factor, especially when that risk factor may impact the other possible sources (another situation in which statistical control is inappropriate, cf. Briere & Elliot, 1993). A case in point involves lead and ethanol, a drug that when consumed excessively by pregnant women decreases intellectual functioning in offspring (Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998). An expanding clinical (Shaper et al., 1982) and preclinical (Nation, Baker, Fantasia, Ruscher, & Clark, 1987; Nation, Baker, Taylor, & Clark, 1986) literature shows that increasing lead burdens increase the volitional intake of alcohol. In such instances what is accomplished by focusing exclusively on the effects of alcohol on IQ and ignoring metal/drug interactions? Lead is no less a risk factor when it acts indirectly to compromise the intellectual apparatus.

1.2. Shortcoming #2 — parental IQ is typically measured poorly or not at all

According to Kaufman, a second shortcoming of the 26 previously published studies is that, while attempting to control for "confounds," parental IQ is typically poorly measured or not measured at all. Kaufman's arguments here are contradictory and illogical. He first criticizes several studies for having used "short forms" of the Wechsler Adult Intelligence Scale but then wrote that "The substitution of a Wechsler short form for the full battery ... is still an acceptable procedure for use in multiple regression analysis and will not adversely affect the outcomes of the study" (p. 313). If the latter is true, then why raise the issue as a concern? Kaufman similarly criticizes the use of the Peabody Picture Vocabulary Test — Revised before pointing out that one could argue that it correlates "highly enough with conventional IQ tests [e.g., $r = .70$ to .80 range] to be an adequate substitute for an IQ test" (p. 314). Kaufman tries to dismiss this argument by noting that the average correlation between IQ the PPVT is somewhat lower [medium $r = .51$] in disadvantaged samples. However, given that in some disadvantaged samples, the correlations were as high as $r = .87$, this is not a convincing argument and it is clear that the PPVT explains a large proportion of the variance in IQ. Thus, when used as a covariate, it partials out a substantial proportion of the variability due to parental IQ and, as noted above, also a substantial portion of the variability due to lead.

1.3. Shortcoming #3 — failure to control for multiple comparisons

Kaufman's third shortcoming was that numerous researchers had performed several analyses without statistically controlling for the number of tests being performed. There are three fundamental problems associated with this argument: (a) it is based on a misunderstanding of the probability of making Type I errors, (b) it assumes that Type I errors are more problematic than Type II, and (c) it ignores the fact that meta-analysis gets around this issue entirely by not calculating significance tests from single studies and, instead, calculating effect sizes across numerous studies. This third problem with the argument may be most critical but, because we discussed it in detail above, we will not discuss it here.

Regarding the first problem, Kaufman seems to have a common misconception about the probability of making Type I errors. It would be beyond the scope of this paper to discuss

this issue in complete detail (see Pollard & Richardson, 1987 for thorough discussion); however, one point is critical to address. Conducting more statistical tests does not automatically lead to more Type I errors, as Kaufman explicitly states. As noted above, one can only make a Type I error when the null hypothesis is true, which in this case means lead does result in IQ loss. The reader may be familiar with the concept of familywise Type I error rate, which can be calculated as $1-(1-\alpha)^k$, where k = the number of statistical tests performed. However, this is a conditional probability, an extrapolation of the conditional prior probability (Pollard & Richardson, 1987), and can be defined as the probability of making at least one Type I error, *when the null hypothesis is true*. Thus, if the null is true and one sets an α at .05, there is a 5% chance of making a Type I error in one analysis. If one performs 10 analyses, and the null is true in every case, then there is approximately a 40% chance of making *one* error out of the 10 statistical tests. However, this probability inflation only occurs when the null is true. If it is false, one cannot make a Type I error.

The second problem with Kaufman's argument is that one should not arbitrarily assume that Type I errors are more problematic than Type II errors (cf. Stevens, 1996), The decision of which to make more important (where to set the alpha level), should be based on the question being addressed. When the issue is health risks in young children, we would argue that minimizing Type II errors would be more important, and using a Bonferroni correction (as Kaufman suggests one *must* do) would radically increase the rate of Type II errors (i.e., concluding that lead is not harmful when actually it is).

1.4. Shortcoming #4 — comparisons of the IQs of the two extreme "lead-level" groups

Kaufman writes that "It is inappropriate to compare the IQs of the two extreme "lead-level" groups when several additional groups are included in the study"(p. 330), claiming that this "violates the rules for interpreting multiple regression analysis" (p. 330). It is our position, however, that Kaufman's assertions are unjustified. As expressed by Lord (1953) years ago, "the numbers do not know where they come from" (p. 751), and as long as the statistical assumptions of multiple regression are met, there is no reason why one cannot perform the analyses that Kaufman criticizes. What has been done is simply an analysis of variance comparing top and bottom groups. Thus, there is no statistical rationale for concluding that IQ losses attributed to lead are "bogus" when comparing extreme groups. Kaufman's contention that regression is only valid for whole samples is simply not true. In actuality, using a dichotomous variable rather than a continuous variable may lead to a lower r^2 value because one has decreased the variability in the predictor variable and it is impossible to predict more variability from less variability[1]. Thus, such a data analytic strategy would lead to an underestimation of the relationship between lead levels and IQ

[1] The one exception would be when there is a strong nonlinear relationship between a predictor and criterion variable. Analysis of the entire sample might obscure the relationship that would only be detected by comparing specific groups. Kaufman speculates that the relationship between lead and IQ loss is nonlinear, but he presents no empirical support for this argument. Furthermore, if he is correct, then multiple regression analyses that did not examine specific groups would have systematically underestimated the relationship between lead and IQ loss.

loss. Perhaps the researcher who only compares extreme groups is making a methodological error, but it most likely will be an underestimate of the actual relationship between blood lead levels and IQ loss.

1.5. Shortcoming #5 — lack of quality control in measuring children's IQ

Kaufman's fifth shortcoming was what he referred to as a "lack of quality control in measuring children's IQ" (p. 28). Here, he is apparently not referring to the quality of the IQ *tests* because he had earlier referred to the "rigorous attempts that most experimenters made to use state of the art IQ tests for *children* [original italics] in the studies" (p. 313). Rather, he seems to be referring to how the tests are administered. However, his argument that the data are questionable because the tests might have been administered by advanced graduate students is not compelling when one considers that extensive training in the administration of standardized intellectual tests is an integral part of graduate training in psychology. Furthermore, even if there were sources of error associated with the administration and scoring of the IQ tests (which certainly is possible), there is no reason to expect that it would be anything other than random error. That is, there is no evidence that there would be more error associated with higher or lower lead level or higher or lower IQs. Thus, as with several arguments discussed above, any unreliability in the dependent variable IQ would simply diminish the effect size for the relationship between lead and IQ loss. Kaufman has once again pointed to a possible way in which the relationship between lead and IQ loss has been *underestimated* by the previous research.

2. Kaufman's overview of the five points

Finally, in an overview that completes Kaufman's coverage of the five principal shortcomings that limit the value of findings in the area of developmental lead toxicity and IQ loss, he returns to the all-important issue of controlling for differences in socioeconomic status (SES). It is within this context that the report by Bellinger, Stiles, and Needleman (1992), is acknowledged to have "... controlled more important SES and family-related variables than any other lead–IQ investigation" (p. 321). Following approbation for exercising excellent control of potentially confounding variables ostensibly overlooked by most other investigators, Kaufman proceeds to challenge the ultimate worth of the Bellinger et al. findings because of shifting norms, statistical violations, and potentially compromising sample characteristics.

It is the Bellinger et al. (1992) sample that invites the greatest criticism in Kaufman's paper. Kaufman accurately notes that virtually the entire sample was comprised of middle-class and upper-middle-class white children who fell into the "high average" range on the WISC-R. Although it is not explicitly stated in the Kaufman paper, the Bellinger et al. findings are tacitly dismissed as unimportant. The argument is that because "... the results of the Bellinger et al. study only generalize to similar samples of high SES white children, not to minorities or to whites from lower social classes" (p. 322), the finding that increased lead levels are associated with an IQ decrement in this study is not a major worry. As noted above,

the results from one study may or may not be generalizable to another sample[2]. However, even if Kaufman is correct about the generalizability issue (and he may or may not be correct), this position, of course, obscures the fact that "upper-middle class white children in the U.S." constitutes a sizable population that merits the attention of public health officials. To be sure, a parent of a child falling into this category would likely want to believe that prophylactic measures would be considered by environmental specialists, and that attempts at improving their child's quality of life were being made. Moreover, the same can be said about Kaufman's expressed concerns over cross-cultural comparisons and generalizability. Restricting statements of generalization to subpopulations defined by millions of children whom may be at risk due to chronic low-level lead exposure can hardly be fashioned as a "... limitation of empirical research."

3. Questionable interpretations of the IQ loss attributed to low-level lead

In addition to suggesting that the developmental lead/IQ literature is fraught with numerous methodological flaws, Kaufman questions the appropriateness of some of the conclusions that have been drawn in this area. That is, even if lead does cause IQ loss, are some of the assertions that have been made justified?

3.1. There is no documented linear relationship between lead level and IQ

Kaufman claims that there is lack of support for a linear relationship between lead level and IQ. Assuming that he is correct, once again he has pointed out how previous research has *underestimated* the relationship between the two variables. That is, multiple regression is based upon the assumption that the relationship between all predictors (which would include all "confounds") and criterion is linear. If the relationship is nonlinear (e.g. quadratic, cubic or higher) a multiple regression equation would *underestimate* the overall relationship between BLL and IQ. Furthermore, Kaufman's statement that "to determine whether the IQ–lead level relationship is linear, the authors of the various studies would have needed to present adjusted IQs for children at each portion of the lead level-continuum" (p. 323) is incorrect. They would only have needed to perform a trend analysis or test for a quadratic or higher order regression effect.

[2] As noted above, Kaufman overstates the problem of generalizability in multiple regression. Often, what does not generalize across samples is the exact variable weights of each predictor, and the more highly correlated the predictors are, the more unstable the weights will be. However, this is different from concluding that what was found to be an important predictor in one sample *cannot* be assumed to be a predictor in another, and research often demonstrates that the findings are indeed generalizable. For example, if one performed a study predicting percent body fat from caloric intake, activity level, and parental percent body fat and all three were found to be significant predictors, would the fact that one used only a sample of high SES adults preclude generalizability to other societal groups? The weights of the individual variables might vary, but all three would still be found to be meaningful predictors.

Kaufman's basic argument here seems to be that there is a threshold effect. However, his only empirical support for this notion was the "eyeball test." That is, he looked at the graphs and concluded that most seemed nonlinear. Apart from the fact that he is not an unbiased rater, his statements regarding his conclusions are ambiguous (e.g., "there was *decidedly* no linearity for children with lead levels below 15 μg/dl"[p. 323] — decided by whom? Or, "The values seem virtually identical" (p. 324) — seems to whom?). Overall, Kaufman's arguments here are not convincing, and we would challenge the reader to perform the same eyeball test of the graphs in, for example, Bellinger et al. (1992).

3.2. Interpreting fractions of an IQ point has no scientific meaning

In this section of Kaufman's discussion, he argues that it is inappropriate to interpret fractions of an IQ point. There are several problems with his argument. First, but less important, his examples are exaggerations. Comparing 1/2 an IQ point to 1/100 of a pound distorts the issue; a better comparison would be to 1/2 a pound. More importantly, the fractions of an IQ point (e.g. .257, p. 304) are per 1 μg/dl; thus with larger increases in lead levels, the issue is not fractions of an IQ point but rather somewhere around 6 IQ points. Most importantly, the reported changes are averages across multiple subjects. Kaufman's example of how meaningful a fraction of a pound would be to one person is misleading because it is based on the individual. Perhaps half of a pound would have little meaning to the individual, but an average of 1/2 pound or, more comparably, six or more pounds *averaged across thousands of people* might have enormous meaning in terms of preventing heart disease, type II diabetes, etc. Kaufman's long discussion of sources of error is interesting, but irrelevant because it is random error that he is describing. It would only be meaningful it he could demonstrate that there was more error associated with high or low IQs or high or low blood lead levels, which he does not do. The bottom line here is that we may be dealing with small effect sizes but as Kaufman himself noted (p. 305), small effect sizes can have practical significance. As noted by Rosenthal (1994) "effect sizes can be of major importance even when they are so small as to have $r^2 = 0.00$." It depends decidedly on the variables being studied; with IQ, average losses of .257 per one μg/dl may indeed have enormous societal consequences.

3.3. Societal consequences of lead level

As indicated by Kaufman, Herbert Needleman and his colleagues have suggested that there will be social and economic backlash consequent to a lead induced displacement to the left in the normal curve that has long characterized the distribution of IQ scores (Bellinger, Stiles, & Needleman, 1992). The idea is that pooling at the lower end of the distribution, coupled with a drain at the upper end, will increase educational costs while depleting the talent base necessary to meet the financial demands of educating greater numbers of impaired children. Kaufman counters with the rationale that Needleman's thinking is flawed because IQ is a relative, not absolute, concept. The abiding theme is that norms change as scores shift within the overall distribution, thus at the extremes the percentages under the curve will remain constant.

To illustrate this point, Kaufman used the example of "an artificial neuronal transmitter that would increase everyone's IQ by 20 points" (p. 326). As with any mathematically operation where a constant is added to every score in the distribution, there would be a shift in the mean but not the variance, consequently the new distribution of IQ scores would have a mean value of 120 in contrast to the previous mean of 100. Yet, because the properties of the normal curve remain essentially intact, the percentages under the curve would remain fundamentally the same. That is, after the restandardization process there still would be 2% at the extremes, etc. Relatively speaking, nothing would change at least as comparisons are made one IQ score to another.

Although Kaufman's argument that IQ is a relative concept is sound from a purely measurement perspective, the illustration is directionally opposite what would be expected regarding developmental lead/IQ interactions. What if there was an event that preferentially altered neurotransmitter function in such a manner that IQ was decreased in the population by a set amount? What would be the consequences in an absolute as well as a relative sense?

In point of fact, there is a burgeoning neurochemical literature that shows lead exposure does alter a neurotransmitter system integral to cognitive and intellectual functioning. In vivo as well as in vitro studies have reliably demonstrated that inorganic lead targets the *N*-methyl-D-aspartate (NMDA) receptor complex, which is a glutamate receptor subtype (Guilarte, 1997; Lasley, Green, & Gilbert, 1999). NMDA receptor activation is known to be essential for biochemical/neurochemical changes that form the basis for learning and memory operations (e.g., Madison, Malenka, & Nicoll, 1991). For instance, hippocampal long-term potentiation (LTP) represents a form of neural plasticity that is thought to be a cellular substrate for learning and conditioning in the mammalian brain (Akhondzadeh, 1999). Inasmuch as lead has been shown to be a potent inhibitor of NMDA-activated LTP (cf. Lasley et al., 1999), it is not surprising that there is a rich preclinical literature that shows a causal connection between developmental lead exposure and impairments in learning and performance (Cory-Slechta, 1997).

Necessarily, understanding the mechanism of action of lead on the developing nervous system has required the use of animal models. But as Rice (1996) points out in her careful review of the commonalities between the available experimental and epidemiological data, there is a remarkable congruence between these two literatures with respect to identifying those processes that determine behavioral deficits. As noted, on p. 313 Kaufman steps away from the experimental literature by stating that "... resolving the causality issue is beyond the scope of this paper." Although this is a reasonable statement, it does not lessen the relevance of emerging parallels between the animal and human data.

In any case, should lead-based disturbances in glutamatergic function, or some other underlying physiologic process related to cognitive ability and performance, actually decrease IQ by a set value, what does this mean in a practical sense? Kaufman is correct in his assertion that in relative terms nothing changes. There are neither fewer nor greater percentages of people who fall at the low end of the curve. The advantaged/disadvantaged ratios will remain the same, so as a population we are no worse off than before. But we are worse off than before. When the ability of an entire population to reason or to respond to changing environmental conditions is compromised, society assumes a definite risk. Within

this context, relative comparisons are meaningless. It hardly matters that a child with a low IQ is no farther behind others in the population than she/he was prior to the introduction of environmental lead. The significant issue is that societal growth is retarded in an absolute sense. The bottom line is that *measurement* of IQ may be in relative terms, but the construct is not. In his hypothetical example of the artificial neurotransmitter that raised IQ points by 20 points, it would be obvious that this had somehow helped the people, even if renormed tests showed their IQs to be the same. Similarly, if lead is lowering IQs, children (and adults) are being harmed. It would seem, then, that we can take little solace from knowing that IQ is a relative concept.

4. Conclusion

In conclusion, Kaufman's statement that "The preceding five points, taken together, represent a rationale for interpreting all of the lead–IQ research, both the positive and the negative findings regarding the impact of low BLLs on IQ, with caution"(p. 320) is perhaps true. However, the caution should be extended at least as strongly if not more strongly in the other direction, i.e., the obtained effect sizes may be underestimates rather than overestimates. Virtually every limitation of the research described by Kaufman points to ways in which the relationship between blood lead level and IQ may have been underestimated. In the final analysis, the converging clinical and preclinical data indicate that even low-level lead exposure can have a profound effect on public health. Human and animal findings consistently point to lead-induced learning impairment (Bellinger et al., 1992; Cory-Slechta, 1997; Rice, 1996), social delinquency and aggression (Delville, 1999; Needleman, Reiss, Tobin, Biesecker, & Greenhouse, 1996), and numerous other disturbances. There is indeed a "trout in the milk" and we believe the bulk of the evidence is very strong in showing that lead threatens early childhood development.

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PERSPECTIVE

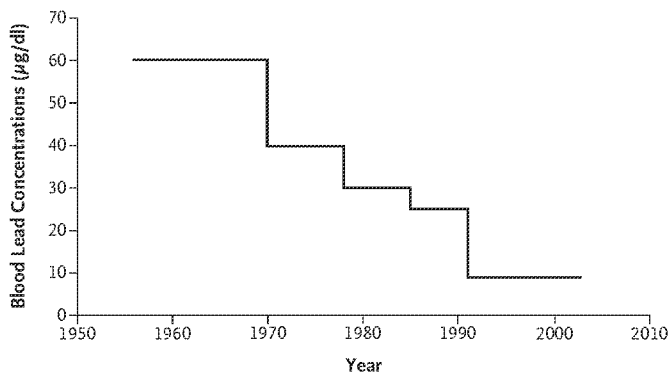
Exposure to Lead in Children — How Low Is Low Enough?

Walter J. Rogan, M.D., and James H. Ware, Ph.D.

Encephalopathy in childhood due to lead poisoning was described more than 100 years ago, and cognitive sequelae after recovery were reported in 1943. During the past three decades, epidemiologic studies have demonstrated inverse associations between blood lead concentrations and children's IQs at successively lower lead concentrations. In response, the Centers for Disease Control and Prevention (CDC) repeatedly lowered its definition of an elevated blood lead concentration, which now stands at 10 μg per deciliter (0.483 μmol per liter) (see Figure). Since the removal of lead from gasoline, the median blood lead concentration in U.S. children has fallen from 15 μg per deciliter (0.724 μmol per liter) in 1978 to 2 μg per deciliter (0.097 μmol per liter) in 1999, a triumph for public health. Yet exposure to lead from deteriorating lead paint in older homes continues; of U.S. homes where children under the age of six years live, 25 percent contain hazardous lead paint. The CDC has estimated that in 2000, there were still 454,000 children in the United States with blood lead concentrations greater than 10 μg per deciliter.

In this issue of the *Journal*, Canfield et al. (pages 1517–1526) extend the unfortunately familiar relation between increased blood lead concentrations and decreased IQ to blood lead concentrations below 10 μg per deciliter. Of 172 children in whom blood lead concentrations were measured serially between the ages of six months and five years, 101 did not have a recorded blood lead concentration above 10 μg per deciliter. Strong and significant associations between blood lead concentration and IQ were observed in these children at both three and five years of age. A smoothed curve summarizing the data shows a decline in IQ of more than 7 points over the first 10 μg per deciliter of lifetime average blood lead concentration and a further decline of approximately 2 points associated with an increase from 10 to 20 μg per deciliter (0.483 to 0.966 μmol per liter).

Although most previous studies have provided little information about children with blood lead concentrations in this range, Canfield and colleagues' findings are a consistent and plausible extension of a very large epidemiologic, clinical, and experimental literature that has indicated adverse effects of lead on cognition. A previous meta-analysis suggested a 2.6-point decline in IQ for an increase in lead concentration from 10 to 20 μg per deciliter.[2] Bellinger et al.,[3] in a study of children with blood lead concentrations closest to those in the current study, estimated a decline of 5.8 points with an increase in blood lead concentration from 10 to 20 μg per deciliter. Although the remarkable steep-



Blood Lead Concentrations Considered to Be Elevated by the Centers for Disease Control and Prevention.

To convert the values for blood lead concentrations to micromoles per liter, multiply by 0.0483. Data are from the Centers for Disease Control and Prevention, 1991.[1]

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ness in the range below 10 μg per deciliter seen by Canfield et al. is influenced by results in 10 children whose blood lead concentrations were near or below 5 μg per deciliter (0.242 μmol per liter) and whose IQs were above 115, it is unlikely that the association is due only to these observations. To confirm the adverse effects of lead on IQ at these concentrations, more children whose blood lead value has never been more than 10 μg per deciliter should be studied.

Lead exposure is more common among disadvantaged children, and so confounding by maternal IQ, socioeconomic factors, and characteristics of the home environment is always a concern. In the study by Canfield and colleagues, however, the association between the blood lead concentration and IQ persisted even after the investigators accounted for several potential confounders by the best available methods. Although critics question the importance of small decrements in the IQs of individual children, these measures are blunt instruments for detecting subtle changes in brain function; any detectable effect occurring from a widespread exposure is cause for concern. Relatively small changes in the mean IQ of a large number of children will dramatically increase the proportion of children below any fixed level of concern, such as an IQ of 80, and decrease the proportion above any "gifted" level, such as 120.

In a second article in this issue, Selevan and colleagues (pages 1527–1536) report that girls from the nationally representative third National Health and Nutrition Examination Survey who had very slightly elevated blood lead concentrations at 8 to 18 years of age had evidence of delayed puberty. Unlike cognitive development, sexual maturation is a relatively new area of investigation for effects of environmental exposures in general and exposure to lead in particular. In the current report, African-American girls with blood lead concentrations of 3 μg per deciliter (0.145 μmol per liter), as compared with girls with blood lead concentrations of 1 μg per deciliter (0.048 μmol per liter), had delays of two to six months in the age at which they attained given stages of breast and pubic-hair development, and four months in the age at which they began to menstruate. Delays were also observed in white and Mexican-American girls, although those associations were not uniformly statistically significant.

Because the study by Selevan et al. was cross-sectional, it remains possible that these findings, if attributable to lead, may be the result of higher blood lead concentrations earlier in life; lead concentrations typically peak in early childhood. Nonetheless, although delays of a few months in the course of puberty are not likely to be a threat to health, these data raise the possibility of an effect on fundamental developmental processes occurring in girls from the general U.S. population at commonly encountered blood lead concentrations. Even though puberty, if delayed by lead, is not delayed by very much, these findings raise the possibility of effects on other hormonally mediated processes.

The effects of lead exposure appear to be long-lasting and irreversible. A previous report in the *Journal* indicated that chelation therapy given to lower moderately elevated blood lead levels in preschool children from environments similar to those studied by Canfield and colleagues had no beneficial effects on tests of cognition, behavior, or neuropsychological function.[4] Prevention is thus the only plausible strategy. Children should not live in housing that exposes them to hazardous amounts of lead, and children who are already exposed need to be identified and their source of exposure interrupted.

The fact that associations seen at these low lead concentrations are subtle is not reassuring; rather, it implies that there is no safety margin at existing exposures. Eliminating elevated blood lead concentrations by the end of this decade is already a federal objective.[5] The new reports underscore the importance of these goals and of the potential consequences of a delay in addressing this entirely preventable condition. They also imply that the job may not be finished even when all children have blood lead concentrations below 10 μg per deciliter.

From the National Institute of Environmental Health Sciences, Research Triangle Park, N.C. (W.J.R.), and the Harvard School of Public Health, Boston (J.H.W.).

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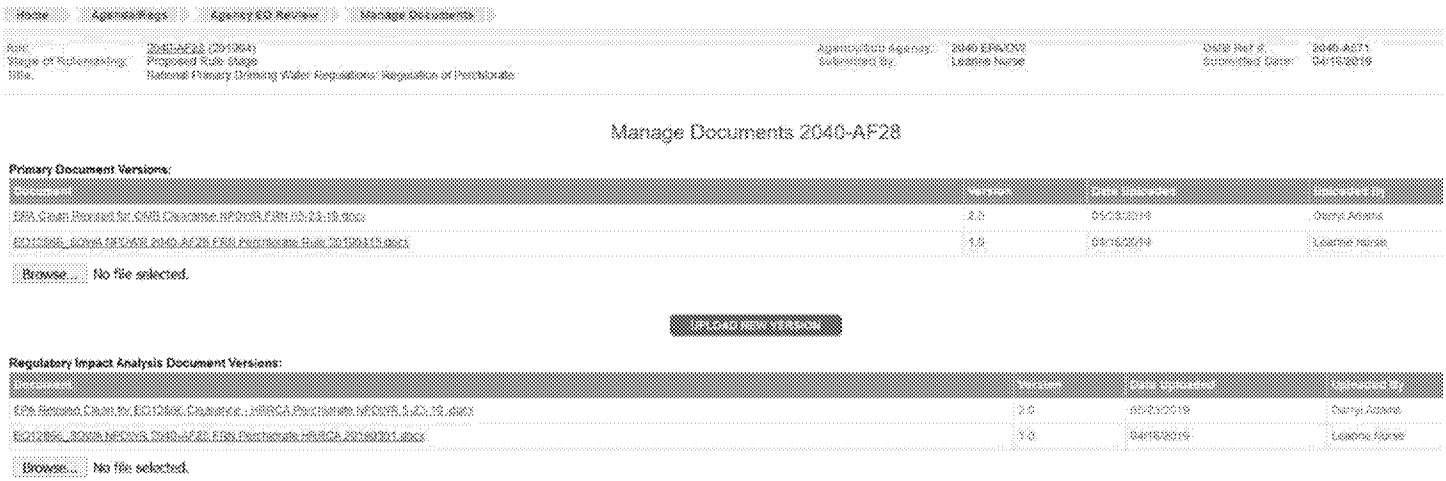
Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 5/23/2019 2:43:04 PM
To: Adams, Darryl [Adams.Darryl@epa.gov]
Subject: RE: Uploaded new versions of Perchlorate, 2040-AF28 into ROCIS

Thanks

From: Adams, Darryl
Sent: Thursday, May 23, 2019 10:42 AM
To: Dorjets, Vlad EOP/OMB <Ex. 6 Personal Privacy (PP)
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Subject: Uploaded new versions of Perchlorate, 2040-AF28 into ROCIS

Vlad et al,
I've uploaded the new versions into ROCIS. Please let me if there are any issues. Thank you.



Darryl Adams
Regulatory Management Division
Office of Policy, U.S. EPA
202 564-6569
Mail Code 1803A, Room 3512D WJC North

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 10/8/2019 3:18:58 PM
To: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
CC: Christ, Lisa (Christ.Lisa@epa.gov) [Christ.Lisa@epa.gov]; Helm, Erik [helm.erik@epa.gov]; Manibusan, Mary [manibusan.mary@epa.gov]
Subject: FW: When you have a moment
Attachments: EO 12866 CLEAN LCRR NPRM 10-8-19.docx

Stephanie:
Per the suggestion below from Mary and Bill, can you please transmit the attached Draft FRN to EPA's OFR office with a request for an expedited review and request an expedited publication date of 10/24. We should note that the document is not yet cleared or signed but that we expect clearance and signature by Thursday.
Eric

From: Manibusan, Mary
Sent: Tuesday, October 08, 2019 10:51 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>
Subject: RE: When you have a moment

Hi Eric,

The perchlorate proposal was received by OP on May 24th and the FRN was submitted to OFR on June 10th with comments and responses delaying the publication until June 26th. With the size of the FRN being 300 pages in length, I would advise sending the document to OFR ASAP, with a request for an expedited review and publication date. As Bill indicated, it is at the discretion of OFR to grant/deny the request, but it will at least flag it as a priority. And as with the proposal, I would anticipate comments from OFR prior to publication. Please let me know if you have additional questions.

Mary

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, October 8, 2019 10:07 AM
To: Nickerson, William <Nickerson.William@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: RE: When you have a moment

Thanks Bill
On 3 we are remembering a one month lag between signature (May 23)and FRN publication (June 26) of the perchlorate proposal which we understood was due to delays in transmitting to OFR. Given the Administrator's aggressive schedule for a final rule (he had us put January in the Reg Agenda) we need to do everything we can to expedite. I realize this may not be sufficient for the OFR but I guess I am checking on what we can do to get this in their queue for publication ASAP. Note that the FRN is over 300 pages in length.
Eric

From: Nickerson, William
Sent: Tuesday, October 08, 2019 9:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>

Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: RE: When you have a moment

I assume 1 and 2 are inevitable.

On 3, we can quickly transmit to OFR and expeditiously deal with any edits that come back. Are you looking for something more than that? It is possible to send a package to OFR with a request to expedite, but OFR is pretty strict about offering a good reason for that (because it's important isn't enough).

Copying Mary in case she has been in contact with OW WPS already on this.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, October 07, 2019 6:33 PM
To: Nickerson, William <Nickerson.William@epa.gov>
Subject: When you have a moment

Bill
I need to check in with you about

1. expedited loading of the final FRN /EA in to ROCIS for the LCRR and
2. expedited processing of the FRN for Autopen signature in time for Thursday's rollout by the Administrator
3. expedited FRN processing following Administrator's signature to assure we don't have a significant lag before publication.

Perhaps the OW WPS staff have already worked this through but I wanted to be certain its on OP's radar.
Can we talk in the morning?
Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Appointment

To: Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]

CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]

Attachments: ORNL TD 01-31-17.docx; BRIEFING BBDR Model Next Steps 01-25-17 _lc (003).docx; Perchlorate_support document_final_05-13-2009.pdf

Location: DCRoomEast2339/DC-ICC-OW-OGWDW; Ex. 6 Personal Privacy (PP)

Start: 1/31/2017 8:00:00 PM

End: 1/31/2017 9:00:00 PM

Show Time As: Busy

Recurrence: (none)

Please find attached 1) draft technical direction for continued support from ORNL/Teresa Leavens, and 2) January 26 briefing for Jen Mclain (OGWDW Acting Deputy Director) on model revision next steps (based on outcome of 1/23 meeting). PLEASE USE THE ATTACHED "BRIEFING BBDR Model Next Steps 01-25-17_lc (003)." SORRY FOR THE CONFUSION, and 3) "Appendix B" discussing variation in renal clearance.

Standing meeting on BBDR model status. Not all people can make all meetings but it is the best time for most people.

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

Code: Ex. 6 Personal Privacy (PP)

Perchlorate BBDR Model Next Steps
January 26, 2017

A. *Tasks needed as input for MCLG approach*

1. Extend model to early pregnancy

Focus on most important life stage sub-model for revisions [pregnant mom 1st trimester]. This will simplify revisions as they will not need to be conducted on other life stage sub-models. Also, Hx is not clinically recognized in lactating moms and infants, but is in pregnant moms, which further supports focus on pregnant mom.

Teresa Leavens (contractor through Pacific Northwest National Laboratory)

- Search for new key references on first term pregnancy parameters
  - Start with Pierce and Lueng citations; Zimmerman study; Merrill study. This will not be a systematic/comprehensive lit review (focus on newer studies).
  - Search terms/data sources: Dietary iodide studies; iodide deficiency studies; NHANES (iodide nutrition); new citations from FDA's TDS

Jeff Fisher (FDA)

- Model parameterization for 1st trimester

Paul Schlosser (ORD)

- Model code

Estimated time to completion: 7 weeks if possible, not confirmed

2. Statistical modeling & quantitative uncertainty/variability analysis

Dustin Kapraun (ORD)/Paul Schlosser (ORD)

- Characterize K_m uncertainty based on Greer et al. data
- Consider other sensitive model parameters to conduct uncertainty analysis
- Explore capabilities of Teresa Leavens to perform analysis

Estimated time to completion: 4 weeks, not confirmed

3. Link BBDR fT4 output to IQ

Abt

- Review, Korevaar 2016, prospective study (n = 3839 mother-child pairs) that provides an association between 1st trimester fT4 and IQ in offspring.
- Assess usefulness for replacing Pop et al (older, smaller study). We may need to obtain raw data from the author to derive an association between the change in fT4 and IQ and revise our approach.
- Discuss in the report.

Estimated time to completion: 3 weeks, not confirmed

B. *Tasks supporting model report*

4. Demonstrate that TSH does not change in response to reduced fT4

Abt/Jessica Georges (TAB)

- Look at NHANES for fT4 and TSH data in the same individual (pregnant and non-pregnant) to check Silva and Silva (1981) assumption that TSH is stable in the Hx range of the model.
- Evaluate if pregnant and non-pregnant populations are similar to increase the size of the useable data set.
- Discuss in report

Estimated time to completion: 4 weeks if possible, not confirmed

5. **Consider co-exposure of thiocyanate and nitrate**
   Jessica Georges (TAB)/Paul Schlosser (ORD)
   - Look at NHANES
     - Does thiocyanate and nitrate levels correlate with perchlorate?
     - Discuss in report

   Estimated time to completion: 3 weeks, not confirmed

Under Interagency Agreement DW89922097-01-0, Work Assignment 2013-02_004, "Health Advisory Program Support," ORNL supported development of a biologically based dose-response (BBDR) model for the hypothalamic-pituitary-thyroid (HPT) axis in nursing and bottle-fed infants and lactating mother for use in dose-response analysis of perchlorate under different dietary iodide conditions.

On January 10 and 11, 2017 EPA's contractor held a public peer review meeting on the BBDR model and draft report. This task directs ORNL to support EPA efforts to implement panel recommendations in developing a sound and defensible BBDR model and report. Specifically, ORNL will support revision of the model report, data extraction and modeling analysis.

Model report revision: Based on external review comments, the report will be focused on modeling of maternal thyroid hormone levels, in particular fT4, during pregnancy, including an extrapolation of the BBDR model to the first trimester. The parts of the report (and appendices) describing development of the lactation model should be moved to a supplemental report. While use of the lactation model for perchlorate dose-response analysis is no longer directly relevant to the dose-response analysis, the model will be needed to refine calibration and evaluate uncertainty in perchlorate and iodide urinary clearance, and on the effect of perchlorate on iodide uptake, by comparison of model predictions to the data of Greer et al. (2002).

After removing the portions of the model report describing the lactation model, the remaining report should be re-organized for clarity. New sections will be required to describe extrapolation to the first trimester, incorporation of parameter uncertainty and variability, and possibly a focused analysis to discuss co-exposure to other goitrogens.

Data extraction: As data are identified to calibrate and evaluate model extrapolation to first trimester pregnancy, the data will need to be extracted to Excel tables and/or .csv files. This extraction shall be accompanied by written descriptions of the data source, extraction method, and any calculation involved, in a corresponding Word document and/or comments in an Excel workbook such that the extraction can be repeated and thereby validated.

Modeling analysis: Supporting model analyses using the computational code may also be requested. A sensitivity analysis of model results vs. model parameters is expected, and to the extent possible this analysis will be combined with an analysis of parameter uncertainty in order to generate measures of overall uncertainty or variability in model predictions. An example of such an analysis and possible source for some data is Lumen and George (2017), Toxicology and Applied Pharmacology 314 (2017) 24-38.

The LOE is 150 hours. No travel is required.

INHIBITION OF THE SODIUM-IODIDE SYMPORTER BY PERCHLORATE: AN EVALUATION OF LIFE STAGE SENSITIVITY USING PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING

U.S. Environmental Protection Agency

Office of Research and Development

EPA/600/R-08/106A

May 2009

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Disclaimer

This document does not represent and should not be construed to represent any final Agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Contributing Authors

National Center for Computational Toxicology
Rory B. Conolly

National Center for Environmental Assessment
Lynn Flowers
Eva D. McLanahan
Jacqueline Moya
Paul M. Schlosser
Paul White

National Health and Environmental Effects Research Laboratory
Mary E. Gilbert

Office of Science Policy
Danielle C. Tillman

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LIST OF ACRONYMS

AAP	American Academy of Pediatrics
AFRL	Air Force Research Laboratory
BW	body weight
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
GW	gestation week
HA	health advisory
HRL	health reference level
IO	Immediate Office
IRIS	Integrated Risk Information System
i.v.	intravenous
LOD	limit of detection
MCLG	maximum contaminant level goals
NCCT	National Center for Computational Toxicology
NCEA	National Center for Environmental Assessment
NHEERL	National Health and Environmental Effects Research Laboratory
NIS	sodium-iodide symporter
NOEL	no-observed-effect level
NRC	National Research Council
ORD	Office of Research and Development
OSP	Office of Science Policy
PA	permeability-area cross product
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
PK	pharmacokinetic
PND	postnatal day
POD	point of departure
RAIU	radioactive iodide uptake
RfD	reference dose
SD	standard deviation
SDWA	Safe Drinking Water Act
SEM	standard error of the mean
TDS	Total Diet Study

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EXECUTIVE SUMMARY

Perchlorate competitively inhibits uptake of iodide by the sodium-iodide symporter (NIS) in laboratory animals and humans. NIS is found in many tissues but is primarily responsible for sequestering iodide from the bloodstream into the thyroid, enabling biosynthesis of thyroid hormones. The National Research Council (2005) advised that the perchlorate reference dose be based on the inhibition of iodide uptake by the thyroid. In this analysis, the physiologically based pharmacokinetic (PBPK) models of perchlorate and radioiodide, which were developed to describe thyroidal radioactive iodide uptake (RAIU) inhibition by perchlorate for the "average" adult (Merrill et al., 2005), pregnant woman and fetus, lactating woman and neonate, and young child (Clewell et al., 2007), were evaluated based on their ability to provide additional information about this critical effect for potentially sensitive subgroups.

The U.S. Environmental Protection Agency (EPA) evaluated the PBPK model code provided by the model authors and found minor errors in mathematical equations and computer code, as well as some inconsistencies among model code files. Office of Research and Development (ORD) scientists made corrections to the code, with agreement from model authors that the corrections should be made, in order to harmonize the models and more adequately reflect the biology.

EPA determined that model parameters describing urinary excretion of perchlorate and iodide were particularly important in prediction of RAIU inhibition in all subgroups; therefore, a range of biologically plausible values available in peer-reviewed literature was evaluated in depth by using the PBPK models. EPA also determined that exposure rates were critical for estimation of RAIU inhibition by the models and thus evaluated exposure rates further.

EPA's analysis identified the near-term fetus (only gestation week 40 fetus could be adequately modeled) as the most sensitive subgroup with respect to percent RAIU inhibition at a perchlorate dose equal to the point of departure (7 μg/kg-day). Specifically, at a perchlorate dose of 7 μg/kg-day, the percent RAIU inhibition predicted by the model for the near-term fetus is 6.7-fold greater than that for the average adult. After correcting the model for reduced urinary clearance in infants, the same analysis predicts percent RAIU inhibition approximately two- to threefold higher for the breast-fed and bottle-fed infant (7–60 days) than for the average adult (differing from Clewell et al. [2007]) and predicts percent RAIU inhibition for the 1- to 2-year-old child about equal to the average adult. Clewell et al. (2007) predicted percent RAIU inhibition in the older child to be about one-half that of the adult; ORD's results are closer to, but still less than, those for the adult.

Overall, detailed examination of Clewell et al. (2007) and Merrill et al. (2005) reflected that the model structures were appropriate for predicting percent inhibition of RAIU by perchlorate in most life stages. Unfortunately, the lack of biological information and data that

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might be used to calibrate key model parameters (in humans of specific life stages) and validate model predictions, particularly for early fetal development, limits EPA's confidence on predictions for fetal endpoints. Therefore, EPA simply chose not to use model predictions for the early- or mid-term fetus. However, because many of the physiological and iodide- and perchlorate-specific parameters in the late-term fetus are expected to be quite close to those of the newborn and there are many more data available for validation of the model in the newborn, the higher confidence in model predictions for the newborn is then partially extended to the late-term fetus (although there is still lower confidence in the late-term fetal predictions than in those for the newborn). Quantitative outputs of the PBPK models as updated by EPA differ by up to threefold from published values, though many of the outputs are within 20% of the published values. Nevertheless, the EPA evaluation determined that, with those modifications as described herein, the Clewell et al. (2007) and Merrill et al. (2005) models are acceptable to calculate the life stage differences in the degree of thyroidal NIS RAIU inhibition at a given level of perchlorate exposure.

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1. INTRODUCTION

The sodium-iodide symporter (NIS) transports iodide from blood into the thyroid gland, enabling biosynthesis of thyroid hormones. Perchlorate is a potent competitive inhibitor of the NIS. Perchlorate has been shown to cause thyroid-related pathologies and neurodevelopmental effects in rodents by disrupting the thyroid axis homeostasis (Gilbert and Sui, 2008; National Research Council [NRC], 2005; York et al., 2005 a, b). NRC (2005) evaluated the human health implications of perchlorate and stated that inhibition of iodide uptake has been unequivocally demonstrated in humans exposed to perchlorate, and it is the key event that precedes all thyroid-mediated effects of perchlorate exposure. NRC advised that the perchlorate reference dose (RfD) be based on the inhibition of iodide uptake by the thyroid. NRC further advised that, while they did not deem iodide uptake inhibition by itself to be adverse, this effect was a precursor to adverse health effects of perchlorate exposure. The lowest dose (7 μg/kg-day) administered in the Greer et al. (2002) study of radioactive iodide uptake (RAIU) inhibition in a group of healthy adult volunteers was considered a no-observed-effect level (NOEL). NRC recommended that the RfD be derived by using this dose as the point of departure (POD), applying an intraspecies uncertainty factor of 10 to account for variability in the human population; fetuses of pregnant women who might have hypothyroidism or iodine deficiency were thought to be the population subgroup of particular concern. The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) adopted NRC's recommendations (U.S. EPA, 2005).

Merrill et al. (2005) described a deterministic, physiologically based pharmacokinetic (PBPK) model for radioiodide and perchlorate and the competitive interaction of perchlorate and radioiodide at the NIS in adult humans. Clewell et al. (2007) extended this work and previous life stage models in the rodent (Clewell et al., 2003a, b) to predict inhibition of the NIS for pregnant and lactating women, nursing infants, and the subsequent stages of childhood.

The following report provides a quantitative analysis of perchlorate-mediated inhibition of the NIS in humans by using the Merrill et al. (2005) and Clewell et al. (2007) PBPK models, focusing on the variability in the degree of NIS inhibition as a function of life stage. This set of models, largely completed after the NRC (2005) report, provides new information that may be useful to EPA for addressing differences in human responses to perchlorate across life stages. The analysis presented here was conducted to inform EPA's regulatory determination for perchlorate under the Safe Drinking Water Act (SDWA). Specifically, the Office of Water requested that staff in the Office of Research and Development's (ORD) National Health and Environmental Effects Research Laboratory (NHEERL), National Center for Environmental Assessment (NCEA), and National Center for Computational Toxicology (NCCT) assist in a thorough evaluation of the Merrill et al. (2005) and Clewell et al. (2007) PBPK models to

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address their scientific soundness and to determine whether or not they are suitable to provide quantitative predictions to the Agency on the life stage variability of perchlorate NIS inhibition of thyroidal iodide uptake.

The evaluation of the PBPK models was conducted in two stages. First, the scientific credibility of the models was evaluated based on the information presented in Merrill et al. (2005) and Clewell et al. (2007), limited inspection of the computer codes of the models, and limited execution of the computer model codes as supplied by the model authors. In concluding this first stage of model evaluation, EPA decided that the PBPK models were potentially suitable to inform regulatory decision making by the Agency, but a more detailed and thorough evaluation of the models was necessary. Thus, the second stage of model evaluation involved a more complete inspection of the computer codes and examination of the technical approach used to develop the model structures and parameter values. In addition, the published models were modified by EPA to fix errors and incorporate new data, particularly data on life stage variability in the urinary clearance of perchlorate, to which NIS inhibition is sensitive.

The first-stage evaluation included staff[1] with expertise in PBPK modeling, developmental neurotoxicology, perchlorate toxicology, and risk assessment. The second-stage, more detailed evaluation was conducted by a subgroup[2] of those who conducted the preliminary first-stage evaluation. The second-stage group consisted of NHEERL, NCEA, and NCCT personnel with expertise in PBPK modeling and in the application of PBPK models to risk assessment, and expertise in developmental neurotoxicology and in risk assessment was retained. The overall approach taken for both the first and the second stages of this evaluation followed the recommendations for evaluation of PBPK models provided by Clark et al. (2004) and Chiu et al. (2007).

PBPK model-predicted inhibition of thyroidal NIS radioiodide uptake by perchlorate was evaluated for several life stages. The PBPK models were developed to evaluate the effect of perchlorate on RAIU inhibition. This was also the dose metric suggested by NRC (2005) as a precursor to the critical effect; thus, the 24-hour RAIU inhibition predicted by the PBPK models was used in this analysis. The life stages evaluated in this modeling analysis included the pregnant woman, fetus, lactating woman, breast-fed infant, bottle-fed infant, 1-year-old and 2-year-old child, "average" adult, and nonpregnant woman of childbearing age. Clewell et al.

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[1] Staff involved in the 1st stage evaluation were as follows:

Hugh Barton, NCCT	Lynn Flowers, NCEA	Eva McLanahan, NCEA
Rory Conolly, NCCT	Mary Gilbert, NHEERL	Paul Schlosser, NCEA
Kevin Crofton, NHEERL	Bob Hetes, NHEERL	Danielle Tillman, OSP
Mike Devito, NHEERL	Annie Jarabek, NCEA/NHEERL	Paul White, NCEA
Hisham El-Masri, NHEERL	Elaina Kenyon, NHEERL	Pamela Williams, ORD-IO

[2] Staff involved in the 2nd stage evaluation were as follows:

Hugh Barton, NCCT	Mary Gilbert, NHEERL	Danielle Tillman, OSP
Rory Conolly, NCCT	Eva McLanahan, NCEA	Paul White, NCEA
Lynn Flowers, NCEA	Paul Schlosser, NCEA	Pamela Williams, ORD-IO

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(2007) developed separate PBPK model codes for the pregnant woman/fetus and for the lactating woman/breast-fed infant. These model codes were provided to EPA by the authors of Clewell et al. (2007). EPA obtained results for the bottle-fed neonate by altering the dose specification in the model for the breast-fed infant. Simulation results for bottle-fed infants were compared to information contained in a consultative letter transmitted from the U.S. Air Force Research Laboratory (AFRL) to EPA (Mattie, 2006). The PBPK model code for the average adult was obtained from the authors of Merrill et al. (2005), while the code for the nonpregnant woman of childbearing age was modified by EPA from the pregnant woman's code by removing the placental and fetal compartments but retaining the mammary compartment.

The PBPK model for each life stage is presumed to represent a typical or average individual from that life stage. Thus, in evaluating specific PBPK parameter choices, especially for urinary clearance, EPA's objective was to ensure that the values appropriately represented an average or central value for a given life stage and age. However, in some cases there is considerable uncertainty on what that average is or should be, and alternative means of predicting the average were considered. In particular, sensitivity analyses were developed by EPA for alternate values of urinary clearance. In the case where more than one alternative clearance value appeared to be equally likely (i.e., had a similar quality and amount of supporting data), then the more "sensitive" option was selected (i.e., the option that leads to predictions of the highest sensitivity to perchlorate-induced RAIU). However, the overall analysis did not seek to select parameters associated with highest predicted effect and is not intended to represent an upper-bound estimate of the average effect of perchlorate in these populations. Again, modeling choices are assumed to represent the best or most likely (central) estimate for an average individual within the population. There is uncertainty about the average, and EPA has selected from within the range of uncertainty, but there is still expected to be population variability around the model predictions based on that choice, with the model prediction being near the center of the distribution.

The PBPK model structures as depicted by Merrill et al. (2005) and Clewell et al. (2007) are shown in Figures 1-1 and 1-2, respectively. EPA's evaluation of model code and modifications did not result in changes to the overall model structure as shown in these figures.

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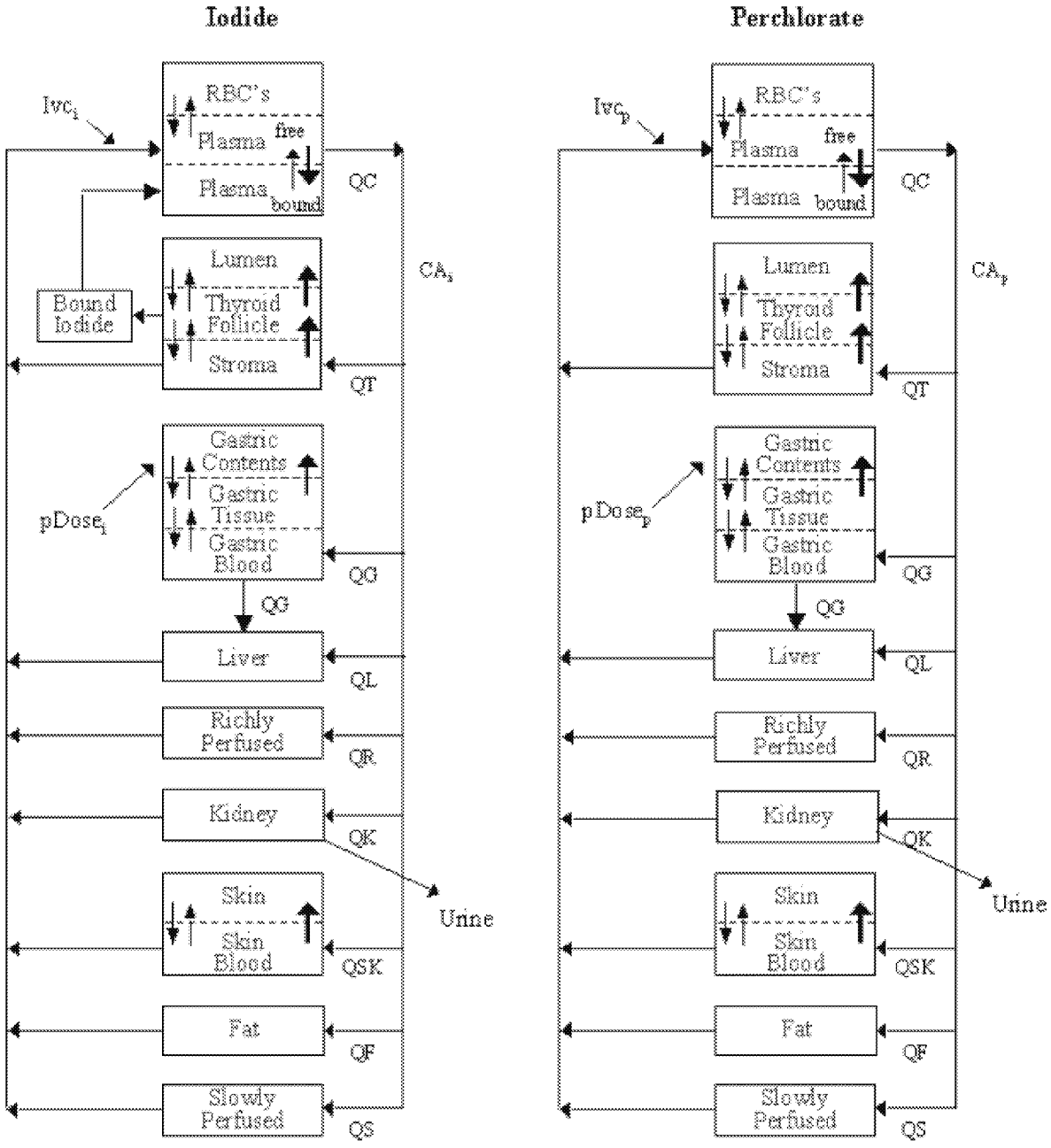

Figure 1-1. PBPK model structure for radioiodide (left) and perchlorate (right) for the average adult.

Bold arrows represent active transport (some compartments; plasma binding also indicated with a bold arrow), double arrows represent passive diffusion, and thin single arrows represent first-order rates.

Source: Merrill et al. (2005). Used by permission. Copyright *Toxicological Sciences.*

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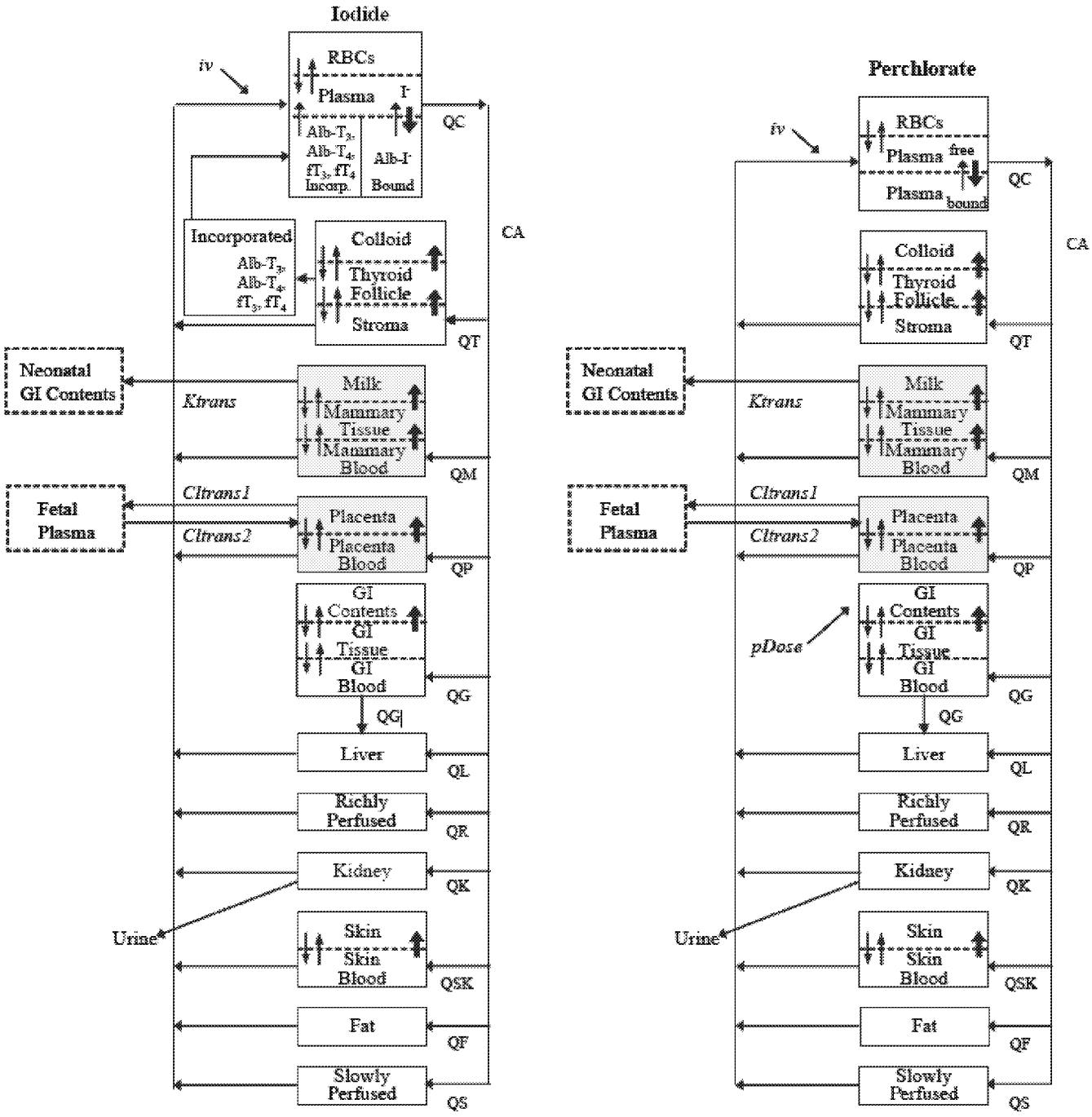

Figure 1-2. PBPK model structure for radioiodide (left) and perchlorate (right) in the pregnant and lactating woman.

The shaded compartments indicate where the model structure differs for infants and neonates. Bold arrows represent active transport (some compartments; plasma binding also indicated with a bold arrow), double arrows represent passive diffusion, and thin single arrows designate first order rates.

Source: Clewell et al. (2007). Used by permission. Copyright *Journal of Toxicology and Environmental Health Part A*.

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2. EXAMINATION OF PBPK MODEL COMPUTER CODE

A number of coding errors were found in each model version/file provided to EPA by the authors (Clewell et al., 2007; Merrill et al., 2005), and several inconsistencies among the various code files were identified. The changes that EPA made to the model code have impacts of varying sizes on predictions of RAIU inhibition. Modeling changes having significant effects are discussed in the text here and/or are shown in Appendix A, section A.4. Except as noted, correction of errors or inconsistencies resulted in only minor changes in model outputs. The model codes, as modified by EPA, were still able to reproduce human data sets shown in Clewell et al. (2007).

An example of a coding error relates to NIS inhibition in tissues other than the thyroid. Inhibition of NIS radioiodide transport by perchlorate was described for the thyroid in all model codes, but other NIS-containing tissues (e.g., gastrointestinal [GI] tract, skin, mammary gland, placenta, and breast (tissue-milk transport)) were found to inconsistently include perchlorate inhibition of radioiodide transport across model codes. Discussion with the Clewell et al. (2007) model authors concluded that the competitive inhibition of NIS radioiodide transport by perchlorate should have been described for all NIS-containing tissues. Thus, EPA added inhibition of radioiodide transport by perchlorate when it was absent in the model codes obtained from the authors.

The model code obtained from the authors of Clewell et al. (2007) for human pregnancy included inhibition of NIS radioiodide transport by perchlorate in the skin and GI tract, but this inhibition was not described mathematically in the model code for the lactating woman, breast-fed neonate, or young child. As noted in Appendix A, section A.4, addition of iodide transport inhibition in the skin had some effect, reducing estimated RAIU inhibition in the average adult model. However, addition of inhibition of NIS radioiodide transport by perchlorate in the skin and GI tract into the code for the pregnant woman did not significantly impact the kinetics or predictions of percent inhibition of thyroidal uptake of radioiodide.

In contrast, the radioiodide excretion into breast milk by NIS in the lactating woman code did not account for inhibition by perchlorate, and inclusion of this inhibition markedly increased the predicted percent inhibition of thyroidal radioiodide uptake in the breast-fed infant. For example, at a maternal dose equal to the POD (i.e., when the mother's ingestion is 7 μg/kg-day), if all model corrections are made *except* that inhibition of iodide transport into breast tissue and breast milk is *not* included, then the radioiodide transport to breast milk is predicted to be *increased* by about 0.3% vs. control due to the inhibition of iodide transport into other maternal tissues. The model then also predicts that thyroid radioiodide uptake by the 60-day-old breast-fed infant (of the mother receiving this perchlorate dose and if the radioiodide exposure also occurs via breast feeding) is decreased by 7.1%, because the inhibition in the infant thyroid from

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the perchlorate he or she ingests more than offsets this small increase in radioiodide ingestion. However, when inhibition of iodide transport in breast tissue and milk is appropriately included in the model, this maternal perchlorate dose is predicted to *decrease* iodide transport into milk by 3.1%, and net predicted inhibition of radioiodide uptake by her 60-day-old infant is predicted to be 10.3%. Thus, correction of this coding error decreased the predicted breast milk transport of iodide, with a nearly additive increase in the net inhibition of radioiodide uptake by the 60-day-old infant thyroid: an impact of 1.5-fold on the effect in the infant. However, these changes also led to a prediction of decreased inhibition in the lactating woman herself, since inhibition of iodide transport into breast milk results in more iodide in maternal circulation and hence is available for maternal thyroid uptake. These and other model code modifications made by EPA are described in detail in Appendix A.

EPA has not identified any coding errors that invalidate the use of the overall model structure of Clewell et al. (2007) for quantitative prediction of perchlorate-mediated competitive inhibition of thyroidal NIS uptake of radioiodide, although EPA predictions with the corrected code differ to some extent from those described in Clewell et al. (2007) as a result of those corrections. EPA has conducted a complete audit of model codes for potential errors. This effort was in support of EPA's in-house analysis of the model code, and a report of the analysis is attached as Appendix C. A PDF document of the model code modified by EPA and used in this analysis is available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199347.

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3. EVALUATION OF PBPK MODEL TECHNICAL APPROACH—DEVELOPMENT AND MODEL PARAMETERIZATION

Because the PBPK models for pregnancy, lactation, and infant/child growth integrate exposure over periods of time when various physiological parameters are also changing, it is helpful to have simple, algebraic equations that describe parameter dependence on gestation week (GW), age, and/or body weight (BW). In several cases algebraic functions were fit to data to evaluate model alternatives (some of which were then used). These curve fits were conducted by using curve-fitting tools available in Microsoft Excel, so the results are reproducible and expected to represent or approximate population-average behavior. However, in most cases the data used were measurement averages or the average together with points at ±1 standard deviation (SD), and thus results would not be identical to what would be obtained if all the original measurement values were available and modeled. However, EPA believes that differences in the quantitative PBPK model predictions between using these curve fits and what might be obtained by more extensive analyses would be small. A strength of PBPK modeling is that model predictions are usually not overly dependent on the precise value of any one parameter: small changes in a parameter or function will not lead to large changes in model predictions. As modifications were evaluated during this exercise, it was indeed found to be the case that slight changes in these curve fits made little difference in model predictions, compared for example to the larger impact of using the "low" vs. "high" urinary clearance options (discussed in detail below).

Good modeling and statistical practice is to use as few parameters as possible to represent a given data set, while capturing the overall *x-y* relationship observed in the data. Therefore, model forms with only two or three fitted parameters but capable of matching the shape of the observed data were preferred. For example, a quadratic model form was used to represent changes in urinary clearance during pregnancy (as observed by Aboul-Khair et al. [1964]) because it was simple, had only two adjustable parameters (with the intercept set to zero), and could be estimated by fitting to data in a Microsoft Excel chart (plot).

EPA's approach was to generate algebraic functions through curve fitting, which would provide good approximations of time- or BW-dependent changes in parameter behavior, using a relatively small number of parameters and simple analytic tools (curve fitting in Microsoft Excel) that could be quickly applied. Advanced statistical methods could be applied but are unlikely to substantially change the resulting model predictions.

3.1. URINARY CLEARANCE

The urinary clearance values for perchlorate and iodide across all life stages were determined to be sensitive parameters for prediction of NIS thyroidal iodide uptake inhibition by

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perchlorate. Thus, urinary clearance was examined further to determine if the approach used in Clewell et al. (2007) appropriately represents the available peer-reviewed literature data on urinary clearance. Details of this evaluation are found in Appendix B, and a brief summary follows.

For parameters based on human data, the following issues were identified. Clewell et al. (2007) scaled urinary clearance of perchlorate and iodide by BW as a function of overall metabolism and clearance ($BW^{0.75}$). This scaling causes urinary clearance per unit of BW to increase as BW decreases. EPA determined, however, that this relationship does not accurately describe the reported rate of urinary clearance in neonates. In fact, several indices of renal function indicate that urinary clearance of perchlorate and iodide in neonates is considerably slower than is indicated by $BW^{0.75}$. For example, glomerular filtration rate (GFR) (normalized to body surface area) in 1-week-old neonates is 11.0 ± 5.4 mL/minute/1.73 m^2, while in infants aged 9–12 months, GFR is 86.9 ± 8.4 mL/minute/1.73 m^2 (Gomez and Norwood, 2005). (Note: A convention in literature reporting these data is to calculate GFR per unit of body surface area [m^2] for the tested individuals but to express the results normalized to a standard adult surface area [1.73 m^2] regardless of the tested individuals' ages.) Data on urinary elimination of a number of compounds, including drugs and drug metabolites, also indicate that renal clearance is slower per unit of BW in neonates (Dorne et al., 2004; Clewell et al., 2002). Modification of the PBPK models to describe slower clearance of perchlorate and iodide in neonates (approximately 50% of adult values when normalized to BW) vs. that described in Clewell et al. (2007) (approximately 200% of adult values when normalized to BW) resulted in an increase in predicted levels of perchlorate-induced NIS inhibition in infants. For example, at a perchlorate dose rate of 7 μg/kg-day (amount ingested by the infant equal to the POD for the RfD), the 7-day-old bottle-fed infant model RAIU inhibition predictions increased from 1.5% (after other corrections were made) to 4.4% (Table 4-2) as urinary clearance decreased.

An analysis of urinary excretion data in children (2–12 years) showed that the default scaling used by Clewell et al. (2007) fell within the range of the data for cimetidine, whose primary clearance mechanism is renal excretion (Lloyd et al., 1985), but the average for those data was better described as scaling by $BW^{1.0}$, resulting in a somewhat lower average predicted clearance (see Appendix B for details). Therefore, EPA chose to estimate perchlorate-induced inhibition by using scaling of urinary clearance proportional to BW for children at 1 year of age and older, which results in somewhat higher estimates of iodide uptake inhibition than reported by Clewell et al. (2007) though still slightly less than predicted for the average adult exposed at the same dose (see Appendix B, including Figure B-4, for additional details). EPA's estimates of urinary clearance in infants and children are lower than those used in Clewell et al. (2007) but are values that EPA judges to be best scientific estimates, not bounds. In particular, the GFR values used for infants were obtained based on the best estimates of statistical fits to experimental data (DeWoskin and Thompson, 2008; Guignard et al., 1975). The clearance

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estimates on which EPA relied were the averaged values presented in DeWoskin and Thompson (2008). The compiled data include those of Guignard et al. (1975); however, considered as a group, the clearance estimates in Guignard et al. (1975) would support lower clearance estimates than the averaged values used here. Thus, it is important to note that the clearance estimates used here are intended to be expected central estimates, and lower (or higher) mean clearance estimates could also be made.

Data were also identified indicating that urinary clearance of iodide by the mother during pregnancy and the first few postpartum months may be as much as two times higher than in the nonpregnant woman (Aboul-Khair et al., 1964). These data include measurements of radioiodide uptake during pregnancy and lactation. Details of the PBPK model analyses with data from Aboul-Khair et al. (1964) are discussed in Appendix B. Model fits using these data also required the assumption of higher maternal NIS levels over this period, which may be consistent with the information indicating higher thyroid activity during pregnancy (Fantz et al., 1999). Some caution is needed in evaluating these data, since the comparisons for pregnancy and nursing were relative to measured adult clearances that were substantially below what is used in the perchlorate PBPK modeling. The reasons for this are not known.

Delange (2004) reviewed data pertaining to urinary clearance of iodide during pregnancy and found studies suggesting both increases and decreases in renal clearance of iodide; thus, urinary clearance changes during pregnancy are inconclusive. In this analysis by EPA and in general pharmacokinetics, clearance is defined as the ratio of the elimination rate (amount/time) to the blood concentration (amount/volume) with units of volume/time and is considered to be the volume of blood "cleared" of the compound per unit of time. Thus, a true evaluation of urinary clearance requires that *both* the urinary excretion rate and the blood concentration be determined, and clearance cannot be determined from only observing urine excretion rates or concentrations. Since it is common and often relatively simple to measure urinary levels of a compound but much less common and more difficult to (simultaneously) measure blood concentrations, it is at least possible that many of the data referred to by Delange (2004) are excretion data rather than clearance data. Since iodide is not metabolized, its excretion would on average equal its ingestion rate in iodide-sufficient conditions; so, even if clearance did change, its excretion would remain the same as long as dietary exposure remained about constant.

Finally, the existing model of Clewell et al. (2007) applies maternal urinary clearance constants for iodide and perchlorate that are about half of the average adult, based on pregnant vs. nonpregnant comparisons in rats, which is the opposite of what the data in Aboul-Khair et al. (1964) suggest and is inconsistent with conclusions by Delange (2004, Tables 1 and 2). While EPA's general preference is to use observations (data) taken directly from humans instead of extrapolating from rats, the fact that baseline adult clearances in this study differ from the model's assumed baseline and that the specific iodide urinary clearance observations of Aboul-

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Khair et al. (1964) differ from the statements of Delange (2004) creates uncertainty around the human data.

Because of these differences in urinary clearance values reported in the literature, EPA considered the following three alternatives for urinary clearance during pregnancy as being equally likely:

1. urinary clearance values reported by Clewell et al. (2007) equal to about half of the average adult
2. increased urinary clearance based on the pregnant:nonpregnant ratio reported by Aboul-Khair et al. (1964)
3. urinary clearance constants assumed to be unchanged in pregnancy from the average adult based on observations of Delange (2004) (see Table 4-2)

To evaluate the impact of this uncertainty, for each case the urinary clearances of perchlorate and iodide were assumed to vary proportionately (i.e., the ratio of perchlorate:iodide clearance constants as estimated in average adults is maintained) (from Merrill et al. [2005]). Unfortunately, perchlorate clearance has not been measured in other human life stages, so there are no human data with which to validate this assumed constant proportionality. The result was that, with adjustments in the fitted parameter representing the thyroid NIS levels, all three assumptions led to equally good fits to the existing data. Therefore, it appears that all three possible cases are equally likely.

Since there are no conclusive human pregnancy data to distinguish which of these alternatives is more likely, EPA selected option 1, the lower clearance values reported in the peer-reviewed paper by Clewell et al. (2007) for relative response estimation (life stage sensitivity analysis), since this value leads to the most sensitive predictions. These lower clearance values were used in producing Tables 4-1, 4-3, and 4-5 below. While this analysis uses the lowest urinary clearance value among the alternatives evaluated, it does not provide an overall upper-bound effect estimate because the impact of uncertainty and variability in parameters other than those examined here (e.g., uncertainty in thyroid NIS parameters and interindividual variability in urinary excretion) was not evaluated.

For lactation, Clewell et al. (2007) used a clearance rate for iodide equal to the average adult but a clearance rate for perchlorate of about 40% of the average adult value, again based on life stage comparisons in rats. However, these values are inconsistent with the values fit to data in lactating rats (Clewell et al., 2003b) and male rats (Merrill et al., 2003) for which the clearance values were almost identical. Further, the data of Aboul-Khair et al. (1964) show an iodide clearance rate that is close to the late pregnancy value immediately following birth but that falls to within control range at postnatal week 12. Thus, EPA again considered three possibilities in a sensitivity analysis:

1. clearance parameters as used by Clewell et al. (2007)

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2. clearance (for both iodide and perchlorate) higher than the average adult, based on Aboul-Khair et al. (1964)
3. clearance equal to nonpregnant average values

In this case option 1 was considered to be less likely than options 2 or 3, since it does not appear to be actually supported by observations (in rats) and it seems biologically unrealistic. There is no known biological basis for perchlorate clearance to be reduced while iodine clearance is not reduced. Simulation results with all three options are shown below in Table 4-2. EPA decided not to use the lower perchlorate clearance of Clewell et al. (2007) (option 1) because of its lack of consistency with available data and because this option was judged to be less plausible. Given the biological uncertainty between setting both clearance values equal to the average adult (option 3) and the higher clearance indicated by Aboul-Khair et al. (1964) (option 2), both options appear to be equally likely, so EPA chose to base the model predictions on option 2, since that leads to the most sensitive predictions. The resulting estimates of perchlorate effects are not upper-bound values, since the options considered were by no means representative of percentiles in a population distribution and this analysis did not address a range of other uncertainties in the modeling, such as uncertainty thyroid NIS parameters and interindividual variability in urinary clearance.

3.2. PARAMETER SCALING

For parameters scaled up from rodents, Clewell et al. (2007) scaled permeability-area cross products (PAs) by $BW^{0.75}$. The use of such scaling is common practice for PBPK model parameters describing metabolic clearance and has been tested through applications with a number of chemicals, although substantial chemical-specific differences from these general scaling assumptions may occur. EPA tested the impact of scaling PA values by $BW^{0.5}$ or $BW^{1.0}$ for most tissues and found that this variation had little impact on predictions of NIS inhibition.

During pregnancy and lactation in the rodent, the placenta and mammary gland tissues undergo size changes that are disproportionate to overall BW. In particular, the placenta volume increases hundreds of times in size over the full course of pregnancy and 16-fold from the end of the first trimester to the end of pregnancy, while total BW increases only about 10%. So even if the scaling power of 0.75 is accepted as being correct, the assumption that the transport parameters in these tissues change with total BW rather than tissue weight appears biologically inappropriate because this assumption leads to the prediction that total NIS levels in the placenta remain approximately constant as the size of the placenta increases hundreds of times.

Therefore, EPA tested the effect of alternate scaling of the chemical-specific placental constants. Specifically, EPA tested scaling of the chemical-specific placental constants by tissue weight rather than total BW, but this scaling approach was found to only result in minimal quantitative changes. However, with the model code as obtained from the authors of Clewell et

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al. (2007), high-frequency oscillations in fetal levels of perchlorate were predicted at the time when the fetal thyroid begins to develop, which was presumed to be biologically unrealistic. Changing the scaling for these constants to depend on tissue weight rather than total BW removed these oscillations. Thus the oscillations appear to result from a numerical instability in the model. Nevertheless, in keeping with EPA's intent to change only those model components that are either clear coding errors or have significant quantitative impact, EPA left these quantities as described in the original code for its reported simulations.

In addition, while the adult woman PBPK code was adjusted by the model authors to reflect changes in body fat and mammary gland size during lactation, the equation used to adjust blood flow to the mammary gland in proportion to its size appeared to be in error, since the flow rate set by it at birth only reflected the mammary gland volume change (increase) during pregnancy rather than the initial (pre-pregnancy) volume plus the increase (i.e., if $V_{M,init}$ is the initial volume and $V_{M,preg}$ is the increase during pregnancy, such that the total volume during pregnancy is $V_{M,total} = V_{M,init} + V_{M,preg}$, the flow rate was set to provide only the flow expected for $V_{M,preg}$ rather than $V_{M,total}$). The result is that the mammary gland blood flow at birth was less than the pre-birth blood flow, even though the tissue volume was greater. The equation was corrected to reflect the total tissue volume at the end of pregnancy/birth.

Finally, the equation and scaling used for binding of perchlorate and iodide to blood proteins are believed to not appropriately reflect the biology. In particular, if the concentration of the binding protein (C_{bp}) is constant across age, as stated by Clewell et al. (2007) and the blood volume (V_B) is a constant fraction of BW (i.e., $V_B = VC_B \times BW$), as is assumed in the model, then the total amount of binding protein should scale as blood (i.e., $A_{bp} = C_{pb} \times V_B = C_{pb} \times VC_B \times BW^{1.0}$). Since the maximum rate of blood binding would be expected to be proportional to the total amount of protein, it then follows that this maximal rate should scale as $BW^{1.0}$ not $BW^{0.75}$ as currently modeled. However, the impact of changing the scaling coefficient from 0.75 to 1.0 was found to be minimal, so the scaling was left in the original form for EPA's subsequent analysis.

Blood binding of perchlorate and iodide is described by using a Michaelis-Menten equation: $r_{bind} = V_{max,b} \times C/(K_{m,b} + C)$, where C is the blood concentration of perchlorate or iodide. In the case where C is approximately constant over a long period of time, as is expected for dietary iodide, this equation would result in a constant rate of binding. However, as the amount of bound material increases, assuming that the *total* concentration of binding protein is constant, the amount of *free* binding protein available would be expected to decrease, which in turn would cause a decrease in the rate of binding. The Michaelis-Menten equation used in the model is qualitatively inconsistent with that mechanistic expectation. Since changing the scaling of this rate had minimal effect on EPA's predictions for tracer radioiodide uptake (where blood concentration is not constant and declines to near-zero levels over a few days), this matter was not pursued further and the model was considered adequate for the evaluation of such tracer

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kinetics. However, if the models were to describe dietary iodide rather than the current trace amounts of radioiodide, describing blood binding by using a Michaelis-Menten equation would not allow for an appropriately variable rate of binding, thus limiting EPA's confidence in using these models for predictions of various intake rates of dietary iodide.

3.3. POSTNATAL PBPK MODELING

Procedurally, to account for exposure to perchlorate throughout pregnancy and hence that the newborn and mother would carry a level of perchlorate from the moment of birth, simulations for both the mother and fetus should first be run by using the pregnancy model to estimate body levels at birth. However, EPA found that, by postnatal day (PND) 7, the predicted fetal and maternal levels had almost no dependence on pre-birth levels vs. exposures that began after birth. Rapid changes in infant thyroid function in the first few days immediately following birth also make the model parameters, and hence model predictions of RAIU inhibition, quite uncertain for those days. Therefore, EPA chose to simulate postnatal exposure, beginning at birth, and to use PND 7 as EPA's earliest prediction.

Key parameters of postnatal exposure are the suckling rates for breast-fed and bottle-fed infants. EPA selected the 90th percentile drinking water intake value for many of the subpopulations evaluated in this report in order to characterize the effects of high-end drinking water exposure to perchlorate. This approach is consistent with the *Guidelines for Exposure Assessment* (U.S. EPA, 1992) and with EPA policies and procedures for deriving health-based drinking water values, including maximum contaminant level goals (MCLGs), health advisory (HA) values, and health reference levels (HRLs). However, for the breast-fed infant, the model explicitly accounts for ingestion by the mother and the child's suckling rate. Therefore, EPA chose to use the 90th percentile ingestion rate for the breast-feeding mother, in which case the perchlorate concentration predicted in her breast milk would represent the high-end consumer but an *average* suckling rate for the breast-feeding infant, since the concentration in the breast milk is reflective of the mother's 90th percentile ingestion rate. Assuming that infant suckling rate and mother's ingestion rate vary independently and using 90th percentile rates for both the infant and the mother would effectively result in an ingestion rate greater than the 90th percentile for the breast-fed infant. This would be inconsistent with the Agency guidelines, policies, and procedures as well as the other life stage evaluations, including bottle-fed infants.

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3.3.1. Breast-Fed Infant Suckling Rate

The suckling rate (breast milk ingestion rate) used by Clewell et al. (2007) was determined to be an inadequate description based on data currently available in the peer-reviewed literature. The original model used a table function to describe the baby's suckling rate, which is a volumetric transport rate (L/h) between the breast milk and baby's stomach, as the route of exposure for perchlorate. Fairly recent data on breast milk ingestion rates (Arcus-Arth et al., 2005) indicate that, in the first couple weeks of life, suckling rates are higher than those set by the table function implemented in Clewell et al. (2007) but are slightly below the table function between 2.5 weeks and several months of age (Figure 3-1). Therefore, to improve PBPK model predictions for the first 2 months after birth, the suckling rate was altered from the original approach used by the authors. A smooth Hill function of infant age (in days) was found to best fit to the mean ingestion rate data from Arcus-Arth et al. (2005) ($r^2 = 0.98$) and was implemented in the description of infant breast milk ingestion:

$$\text{Milk Ingestion Rate (mL/h)} = \text{KTRANS} = \frac{28.4 \times Age_Days^{2.4}}{3.06^{2.4} + Age_Days^{2.4}}$$

This equation is not used to describe the breast milk ingestion beyond the first two months of age, the point at which the ingestion rate begins to decrease.

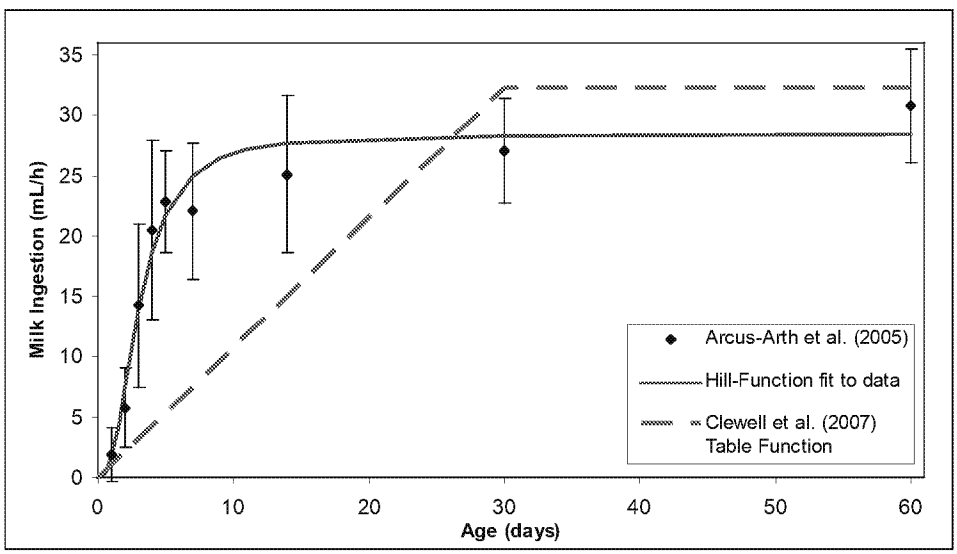

Figure 3-1. Breast milk ingestion values used by EPA.

Prior to the plotting of data from Arcus-Arth et al. (2005), the data were converted from g/kg-day to mL/h by using model-derived BWs at the given ages (BWs were not provided in Arcus-Arth et al. [2005] for all life stages).

Data source: Arcus-Arth et al. (2005).

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In addition, while iodide uptake inhibition in the infant was estimated by Clewell et al. (2007) using a simulated radioiodide injection directly to the infant, that approach would not account for the effect of maternal perchlorate exposure on iodide ingestion by the infant in breast milk. The model code already described iodide transport to breast milk; however, EPA added perchlorate inhibition of that transport, as noted above. Additionally, the model was extended to allow for transfer of the breast milk iodide to the breast-fed neonate's stomach (using the same suckling rate as for perchlorate) and estimated total infant thyroid iodide at 24 hours after simulated intravenous (i.v.) injection in the mother as the measure of effect. No change was needed for the bottle-fed infant, since the amount of iodide in the formula was presumed to be unaffected by the presence of perchlorate. Predicted radioiodide kinetics in infant blood was much different under this scenario, with a slower rise and fall and a peak around 12 hours after maternal injection. Thus, some of the dissimilarity between bottle-fed and breast-fed infant predictions can be attributed to this difference in radioiodide kinetics.

It should also be noted that, for breast-fed infant simulations under the RAIU inhibition scenarios being evaluated, the i.v. dose of radioiodide was treated as being given to the mother, a portion of which passed to the infant through breast milk. The portion passing to the infant in the absence of perchlorate served as the control value. So, in addition to the inhibition of iodide uptake by the infant's thyroid predicted by the model, the ingestion of perchlorate by the mother inhibited iodide transport into the breast milk, thus accounting for a perchlorate-induced alteration in nutritional iodide. The reduction of iodide transport in milk was small in the sense that the predicted reduction was only 0.7–1.0% when the infant was receiving 7 μg/kg-day of perchlorate (for infants between 7 and 60 days old, with maternal perchlorate clearance at the average adult value). But this reduction had a near additive effect on the predicted reduction of iodide uptake by the infant's thyroid at this dose rate, which was 2.5% in the 60-day-old bottle-fed infant (see below) but 3.5 % for the breast-fed infant of the same age (both obtained by using the lower infant clearance, based on glomerular filtration but adult-average maternal clearance).

3.3.2. Bottle-Fed Infant Model Simulation Approach

The model code for the breast-fed infant was modified to allow for exposure to perchlorate via ingestion of a water-based formula rather than breast milk. This provided for direct comparison of a bottle-fed infant with a breast-fed infant by using the same PBPK model structure and parameter set but with an alternate exposure scenario. Briefly, the lactating mother's perchlorate dose rate was set equal to zero, which allowed the infant's perchlorate exposure to be controlled independent of the mother's. The model was coded such that a fixed dose of perchlorate could be administered to the infant or a water concentration could be multiplied by a formula ingestion rate. Also, a direct i.v. dose of radioiodide to the bottle-fed infant was used in the determination of perchlorate inhibition of iodide uptake. The presence of

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perchlorate in formula is assumed not to decrease the iodide available to the infant in the formula. More details of this approach are included in Appendix A.

To account for the fact that water ingestion varies with age and BW in the bottle-fed infant, a smooth function of age was fit to the results of Kahn and Stralka (2009), which had been plotted against the midpoint for each age range, as shown in Figure 3-2A. However, to account for the minimal ingestion occurring in the first couple days of life, the equation was multiplied by a rising exponential function: $1 - e^{-day}$. Note that the function describes the BW-specific ingestion rate (L/kg-day), so it is multiplied by BW to obtain the total ingestion (L/day), which is then a continuously increasing function of age, as shown in Figure 3-2B. (The function is only used for predictions up to 60 days of age.)

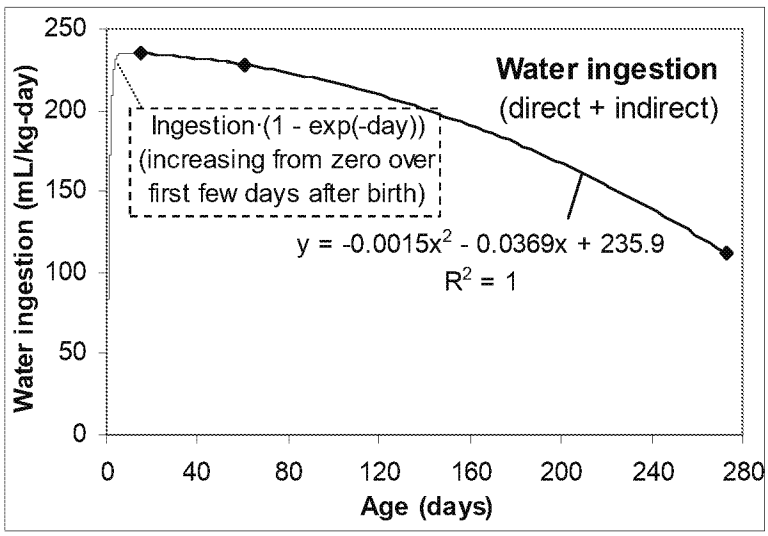

Figure 3-2A. Ninetieth percentile water consumption values used by EPA for the bottle-fed infant.

BW-specific function (mL/kg-day) shown as fit to 90th percentile water ingestion data from Kahn and Stralka (2009).

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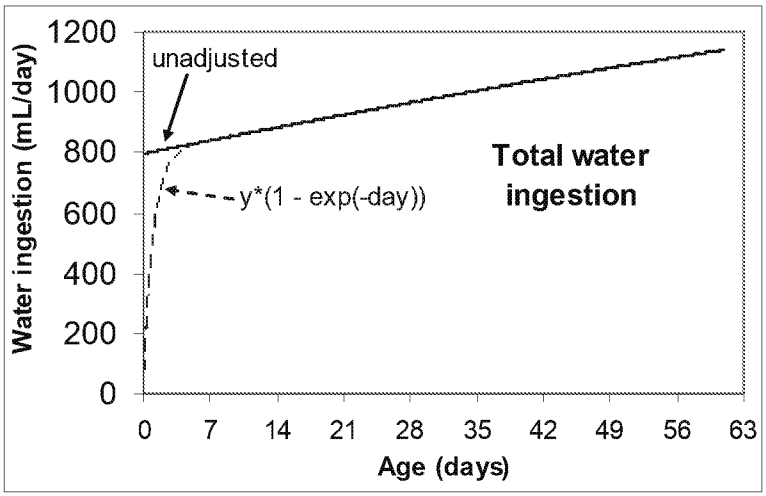

Figure 3-2B. Ninetieth percentile water consumption values used by EPA for the bottle-fed infant.

Plot of total ingestion (mL/day), calculated by multiplying age-specific ingestion rate (mL/kg-day) from Figure 3-2A by age-specific BW (kg).

A detailed description of issues with parameterization and coding errors in the PBPK models and the resolution of these issues is provided in Appendix A.

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4. PBPK MODEL RESULTS AND LIFE STAGE ANALYSIS

4.1. PBPK MODEL RESULTS

Table 4-1 compares model predictions published by Clewell et al. (2007) with predictions for the model incorporating EPA's corrections to equations and parameters—with the important exception that the urinary clearance rates in the published model are retained here. This analysis is intended to show the impact of the various other changes EPA made to the model. The two sets of values are generally close with the exception of the lactating mother, in which model predictions are approximately one-third of the values previously published in the lower dose range. This change is primarily due to the corrections in model code whereby inhibition of iodide transport into maternal skin and particularly breast tissue/milk by perchlorate was added to the code. Adding these terms leads to the prediction that, with perchlorate exposure, more iodide is kept in the circulating maternal blood rather than being transported to skin or transferred to the infant. Hence, more is available for uptake by the thyroid, reducing the impact of perchlorate inhibition of thyroid uptake.

Table 4-1. Comparison of Clewell et al. (2007) published model predicted percent inhibition of thyroidal radioiodide uptake across life stages with EPA modified versions (but retaining the Clewell urinary clearance rates)*

External dose (mg/kg-day)	Fetus[a] (% inhibition)		Breast-fed neonate[b] (% inhibition based on dose to mother)		Child[c] (% inhibition)		Pregnant woman[a] (% inhibition)		Lactating woman[d] (% inhibition)	
	Clewell	EPA	Clewell	EPA	Clewell	EPA	Clewell	EPA	Clewell	EPA
0.001	1.1	1.3	0.9	1.9	0.3	0.3	1	0.92	1.1	0.60
0.01	10	11	8	17	3	2.7	9	8.5	10	6.0
0.1	49	51	34	68	21	22	50	49	54	43
1	84	85	63	95	72	74	91	90	92	89

*For this comparison, infant and maternal urinary clearance rates were set as in Clewell et al. (2007).
[a]Fetus and pregnant woman shown at GW 38 using clearance values as published in Clewell et al. (2007) that are equal to about half of the average adult value.
[b]Breast-fed neonate shown at postnatal month 1.5 (day 45). External dose is that ingested by the mother. Neonate ingestion (mg/kg-day) is 4.4, 4.1, 2.6, and 0.85 times maternal ingestion at external doses of 0.001, 0.01, 0.1, and 1 mg/kg-day, respectively, due to saturation of NIS-mediated transport of perchlorate into breast tissue and milk at higher doses.
[c]Child shown at 7 years of age with the EPA prediction using "medium" estimate for urinary clearance.
[d]Lactating woman shown at PND 7.

Table 4-2 compares the effects of alternate urinary clearance parameters on the EPA-modified PBPK model predictions of RAIU inhibition for the different life stages. A decrease in the PBPK model urinary clearance rate of iodide and perchlorate resulted in increases of RAIU inhibition predictions for all life stages. The largest effect was seen for the near-term fetus

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(GW 40), such that the prediction of fetal RAIU inhibition increased from 3.4% inhibition at the highest rate of clearance to 11% inhibition at the lowest rate of clearance (Table 4-2). The detailed effects on RAIU inhibition resulting from the EPA model modifications, some of which are described in section 3, are provided in Appendix A.

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Table 4-2. Effect of urinary clearance on model predicted percent inhibition of thyroidal radioiodide uptake at the POD (7 µg/kg-day) for various life stages, using the EPA version of model code

Urinary clearance rate	Gestation model[b]		Lactation model[c]									Older child[f]	
	Pregnant woman	Fetus	Lactating woman[d]			Breast-fed infant (based on dose to infant)[e]			Bottle-fed infant[c,e]			10 kg	14 kg
	GW 40	GW 40	7d	30d	60d	7d	30d	60d	7d	30d	60d	0.97yr	2yr
High	1.6%	3.4%	1.3%	1.7%	1.9%	2.8%	3.0%	3.3%	1.4%	1.5%	1.5%	1.3%	1.3%
Medium[a]	2.9%	5.2%	2.1%	2.0%	2.0%	3.1%	2.8%	2.9%	1.8%	1.3%	1.2%	1.7%	1.7%
Low	6.1%	11%	4.4%	4.0%	4.0%	6.2%	4.4%	4.2%	4.3%	2.9%	2.5%	2.1%	2.1%

[a]Average adult value for urinary clearance (clearance constants $CLUC_I = 0.11$ and $CLUC_P = 0.125$) was used as a "medium" estimate for the pregnant and lactating woman and the older child..

[b]"High" value for urinary clearance was determined from Aboul-Khair et al. (1964) and $cluc_i = (1 + 0.0703 \times GW - 0.0012 \times GW^2) \times 0.11$ and $cluc_p = (1 + 0.0703 \times GW - 0.0012 \times GW^2) \times 0.125$, where GW = 40. The V_{max} for thyroidal uptake of iodide and perchlorate were adjusted ($V_{max}Tc \times 1.8631$) to fit Aboul-Khair et al. (1964) maternal thyroid uptake data (more detail in Appendix B). Fetus percent inhibition of RAIU was affected by maternal urinary clearance and thus included in the table; however, no fetal parameters were altered. Maternal NIS V_{max} values were not readjusted for the medium clearance. "Low" value for urinary clearance was used as published in Clewell et al. (2007) where $CLUC_I = 0.06$ and $CLUC_P = 0.05$, determined from the parallelogram parameterization approach.

[c]The initial conditions used to estimate the percent inhibition of thyroidal radioiodide uptake for the lactating woman and breast- and bottle-fed infants were set at the final pregnant woman and fetus values by using the medium clearance rate.

[d]High clearance rate for the lactating woman was set equal to that of the average adult values from Merrill et al. (2005), but the V_{max} for thyroid perchlorate and iodide uptake was adjusted to fit literature data. Central estimate did not include V_{max} adjustment. The low estimate was as published by Clewell et al. (2007), where the clearance for iodide was equal to the average adult but the clearance rate for perchlorate was about half ($CLUC_P = 0.05$).

[e]The dose to the lactating woman was adjusted so that the breast-fed infant received a total dose of 7 µg/kg-day perchlorate from maternal milk. Maternal dose rates lower than the POD were needed to provide 7 µg/kg-day to the infant, as follows in µg/kg-day: high maternal clearance at 7 days, 4.3; 30 days, 3.8; and 60 days, 3.9; medium maternal clearance at 7 days, 2.7; 30 days, 3.0; and 60 days, 3.6; and low maternal clearance at 7 days, 1.1; 30 days, 1.5; and 60 days, 1.8. The bottle-fed infant was simulated by using a constant 7 µg/kg-day perchlorate dose rate. High is estimated by using $BW^{0.75}$ scaling as published in the Clewell et al. (2007) model. Medium assumes that clearance is equal to GFR (i.e., $CLUC_I = CLUC_P = [7.5\ L/h]/[70^{2/3}]$, with a scaling coefficient of 2/3). Low assumes that clearance/GFR is the same as in the adult (≈40%). V_{max} for thyroid iodide uptake was adjusted for all clearance rates to fit literature data shown in Clewell et al. (2007, Figures 5 and 9).

[f]High value was estimated as published in Clewell et al. (2007) by using iodide and perchlorate urinary clearance constants equal to the average adult and the constants were scaled by $BW^{0.75}$. Medium used the same constants but scaled by $BW^{1.0}$; this scaling described the average renal excretion of cimetidine (Lloyd et al., 1985) better. The low clearance was estimated by scaling by $BW^{1.0}$ and multiplying by the ratio (0.76) of the lower 95% confidence bound to the mean for the Lloyd et al. (1985) data.

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4.1.1. PBPK Model Predictions Compared with Literature Data

EPA-modified PBPK model predictions were compared with recent literature data as well as data previously simulated by Clewell et al. (2007) and Merrill et al. (2005). These comparisons of model data with literature data are detailed in the sections below.

4.1.1.1. *BW Change During Pregnancy*

The Clewell et al. (2007) gestational model prediction of BW change during pregnancy was compared with literature data that were not used to develop the growth equations. While the Centers for Disease Control and Prevention collects data on maternal weight gain and other health indicators for pregnancy, these data appear to be reported as total weight gain (from conception to just before birth), reported in the form of percent of population falling into various categories ("underweight," "normal weight," etc.) and do not include information on specific growth. However, Schieve et al. (2000) reported BW gains during pregnancy from data for 3,511 mother-infant pairs from the 1988 National Maternal and Infant Health Survey, and Wolfe (1993) provided "upper-limit" and "lower-limit" values for ideal weight gain during pregnancy. These data were compared with the model-predicted BW gain (Figure 4-1).

Except for the apparent plateau in the data starting around GW 38, the shape of the model growth curve matches the observed growth curve quite well. While the curve falls somewhat below the observed mean (Schieve et al., 2000), it is well within one SD of the mean. Considering that these were data not used in specifying the model, the agreement appears to be quite good.

The data for the last few time points represent women who had not already given birth by that time (e.g., women who gave birth at GW 40 would not be included in the population represented at GW 42). So the apparent plateau should not be construed to mean that an individual woman's BW would plateau or begin to decline in the last few GWs. Rather, it likely indicates that women who had the highest increase in BW by GW 38 (when the peak in the mean value occurs) gave birth in that week and so were not included in the population analyzed at later weeks. Since there is a tendency to induce labor before the child becomes too large to be safely delivered, the downward trend is then explained as a population shift, whereas the model growth curve represents the change in a particular individual.

Finally, to test the sensitivity to BW, an alternate model version with the growth curve shifted upward (Figure 4-1) was tested and compared to the original model. RAIU inhibition was evaluated at GW 40, given an exposure to 7 μg/kg-day perchlorate (the POD). With the model growth curve as specified by the authors (Clewell et al. 2007), the RAIU inhibition predicted for the mother and fetus were 6.10 and 11.0%, respectively, and, with the BW increased to better match the observed mean, the model predicted 6.14 and 11.1%, respectively. Thus, the sensitivity of model predictions to changes in this range is negligible.

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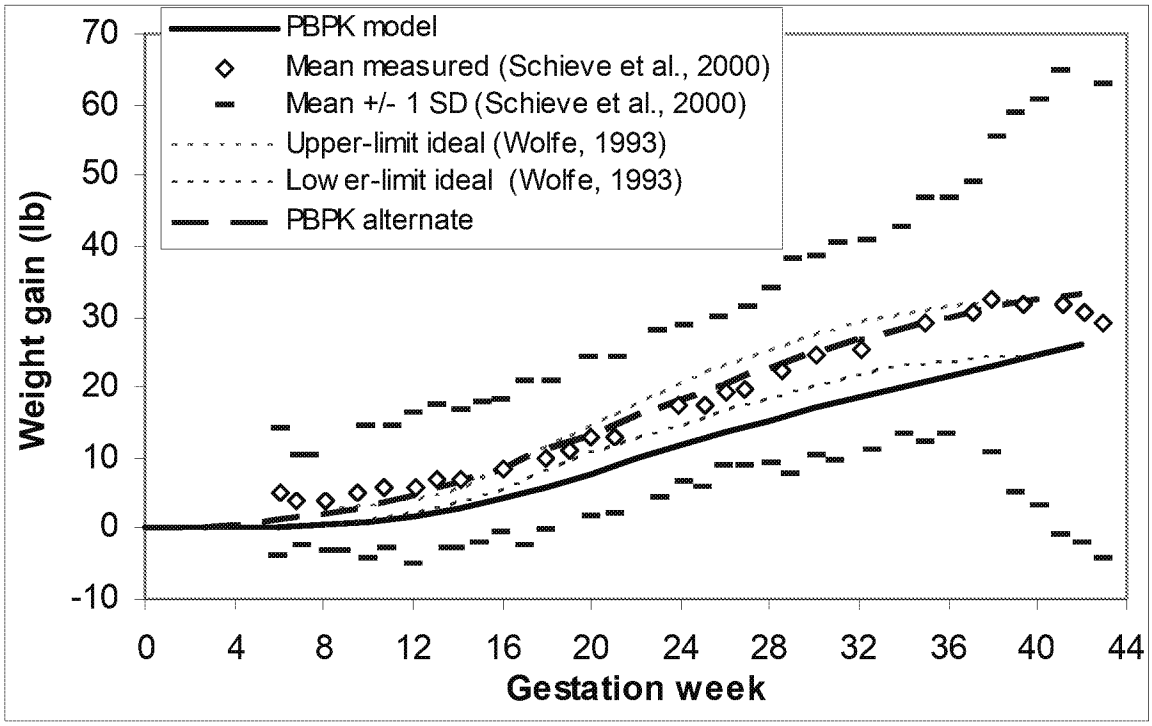

Figure 4-1. Weight gain during gestation as predicted by the PBPK model equations implemented by Clewell et al. (2007) compared with recent literature data.

The BW gain predicted by the PBPK model is within one SD of the mean data throughout gestation, with the best correlation at GWs 36 to 40.

4.1.1.2. *Perchlorate and Iodine in Breast Milk*

For this exercise, the mean breast milk iodide for breast milk perchlorate concentrations less than 20 µg/L was considered to be "control" and estimated to be 199 µg/L by digitizing data from Pearce et al. (2007, Figure 1). Because the PBPK model does not simulate dietary iodide, the PBPK model-predicted 24-hour inhibition of radioiodide transfer into breast milk ($\%BM_{inh}$) was converted to a value relative to the Pearce et al. (2007) data by using the following calculation: $(100 - \%BM_{inh}) \times 199\ \mu g/L \div 100$. For example, when the model predicted breast milk perchlorate to be 100 µg/L, a corresponding 3.3% decrease in 24-hour radioiodide in breast milk was observed: $(100 - 3.3) \times 199\ \mu g/L \div 100 = 192\ \mu g/L$. When the model predicted breast milk perchlorate concentration to be 334 µg/L, a corresponding 11% inhibition in breast milk 24-hour radioiodide was predicted. This value falls within the range of the Pearce et al. (2007) data, and thus the model predictions appear to be in line with the epidemiology data (Figure 4-2).

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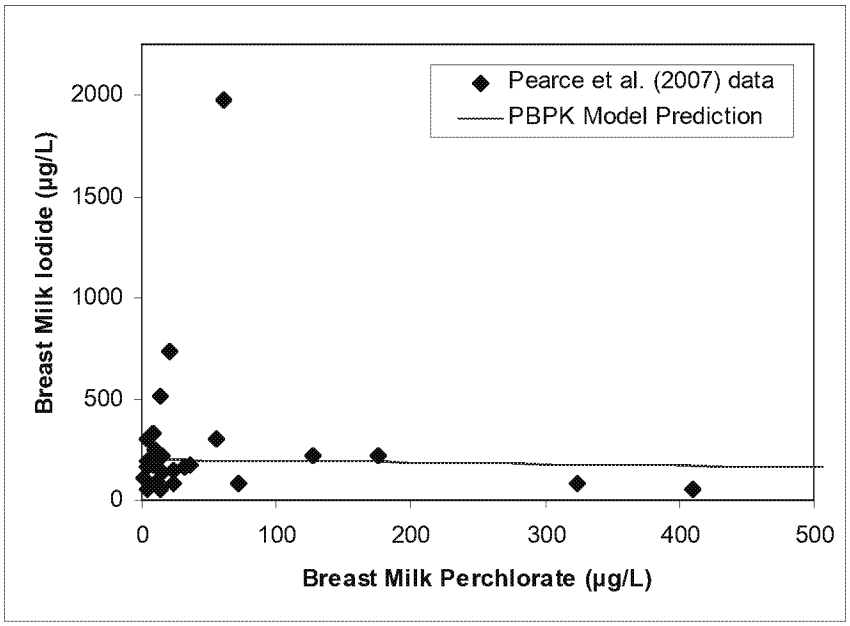

Figure 4-2. PBPK model prediction of breast milk perchlorate and iodide compared with data from Pearce et al. (2007).

The PBPK model was used to predict perchlorate concentration in breast milk and reduction in breast milk radioiodide concentration at 48 days post partum (median from Pearce et al. [2007]), using a range of perchlorate oral dose rates (1–50 µg/kg-day).

4.1.1.3. *Comparison with Data Previously Simulated by Merrill et al. (2005) and Clewell et al. (2007)*

The following sections show comparisons of data with a few simulations, using the EPA-modified PBPK models for the average adult (Merrill et al., 2005) and gestation, lactation, and older child life stages (Clewell et al., 2007). Data in the figures below correspond to figures in the original model publications by Merrill et al. (2005) and Clewell et al. (2007). The modified PBPK model versions used by EPA in this evaluation remain in agreement with kinetic data shown in the original manuscripts and previously compared with the Merrill et al. (2005) and Clewell et al. (2007) PBPK models for radioiodide and perchlorate.

4.1.1.3.1. ***Average adult.*** The EPA-modified PBPK model for the average adult was tested for its ability to predict data shown in figures presented in Merrill et al. (2005). A few of the model simulations compared with observed data are shown below in Figures 4-3 and 4-4.

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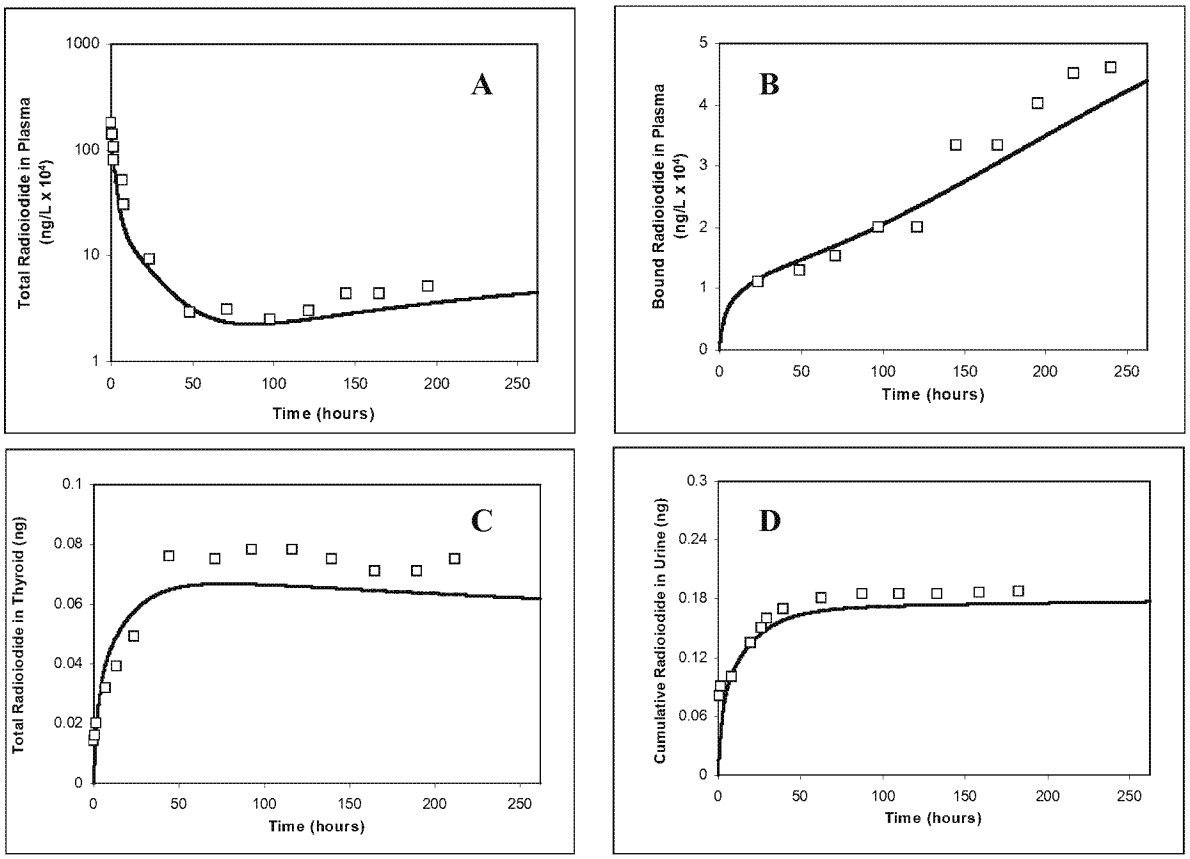

Figure 4-3. EPA-modified PBPK model simulations for radioiodide in the average adult.

Model simulations (lines) shown with measured radioiodide (points) for (A) plasma, (B) protein-bound radioiodide in plasma, (C) total radioiodide in thyroid, and (D) cumulative radioiodide in urine after a tracer radioiodide i.v. dose at time zero. Similar simulations were originally shown in Merrill et al. (2005, Figure 3).

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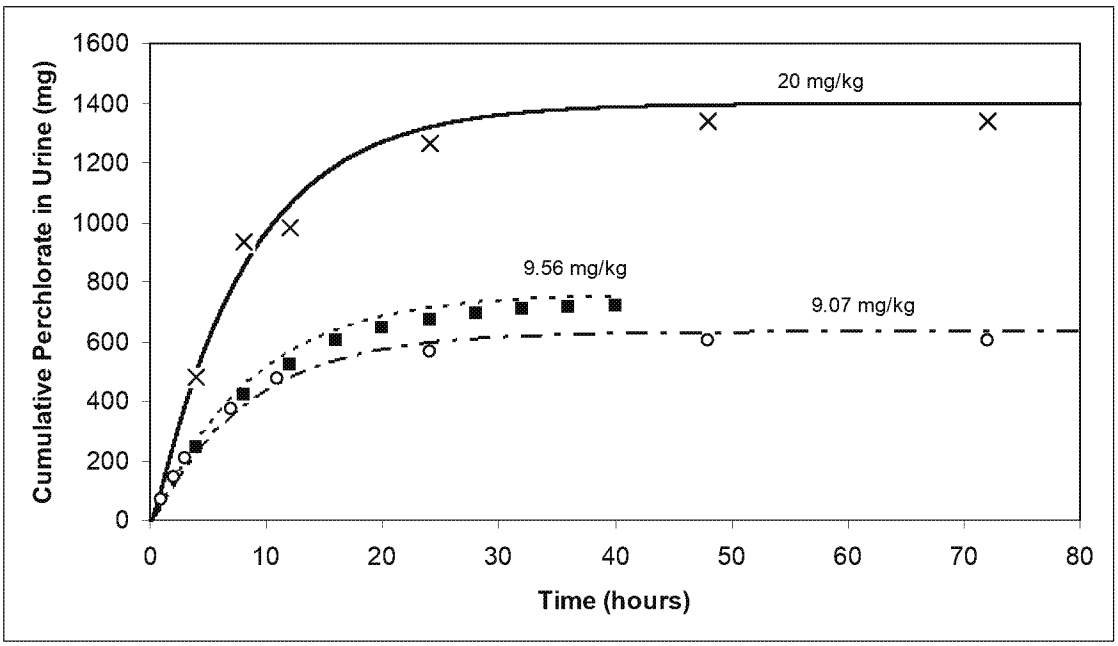

Figure 4-4. EPA-modified PBPK model simulations for perchlorate excretion by the average adult.

Model simulations (lines) shown with cumulative urinary perchlorate (points) measurements. Simulations correspond to figures originally shown in Merrill et al. (2005, Figures 8–10). Perchlorate oral bolus doses (9.07, 9.56, or 20 mg/kg) were administered to healthy male volunteers at time zero, and urinary perchlorate was measured at various times following dose.

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4.1.1.3.2. ***Pregnant woman and fetus.*** The EPA-modified PBPK model for the pregnant woman and fetus was tested for its ability to predict data shown in figures presented in Clewell et al. (2007). A few of the model simulations compared with observed data are shown below in Figures 4-5 and 4-6.

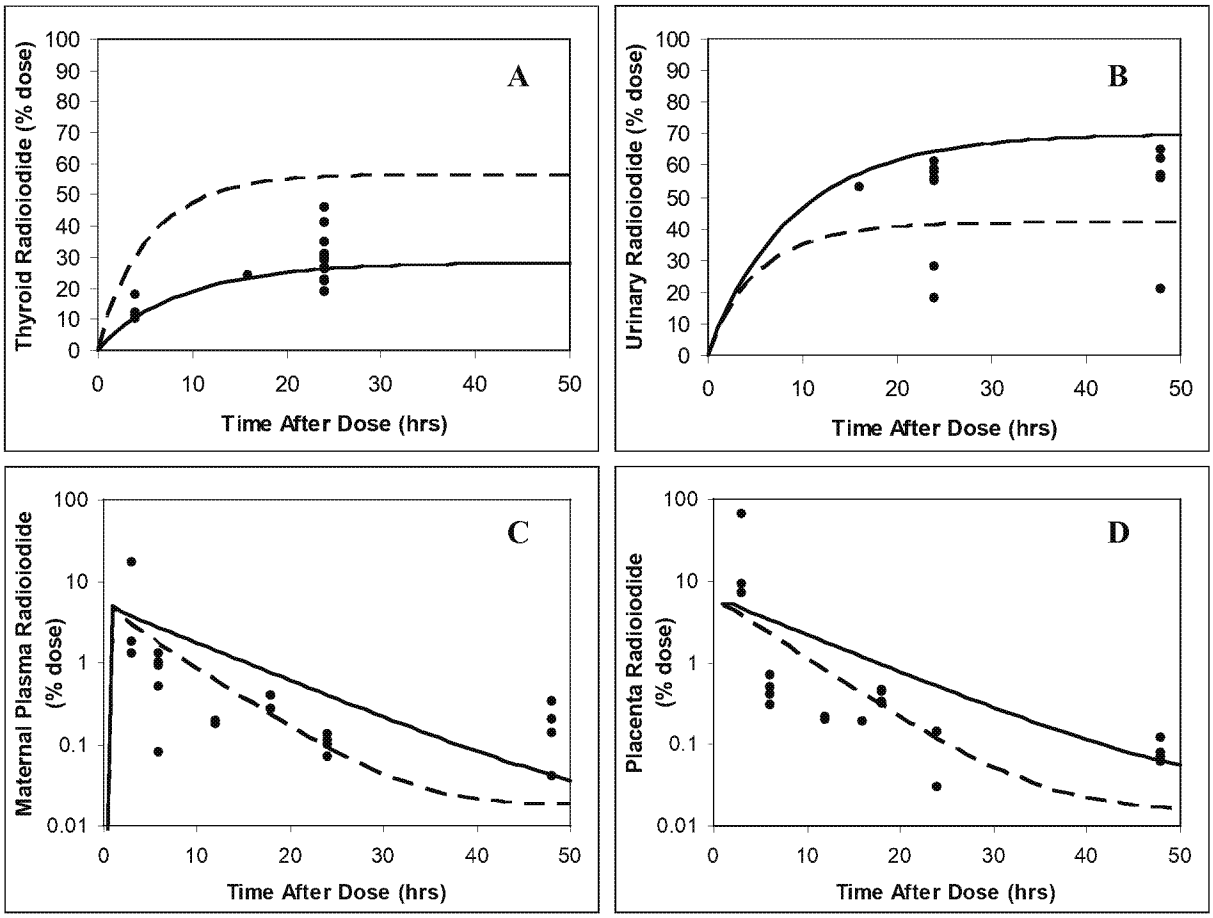

Figure 4-5. EPA-modified PBPK model simulations of radioiodide in the pregnant woman at GW 22.

Model simulations (lines) shown with measured radioiodide (points) for (A) total radioiodide in thyroid, (B) cumulative excretion in urine, (C) maternal plasma, and (D) radioiodide in the placenta after a tracer radioiodide i.v. dose at time zero. Similar simulations were originally shown in Clewell et al. (2007, Figure 6). As in Clewell et al. (2007), the solid and broken lines indicate the model simulation using thyroid NIS iodide V_{max} mean (1.22×10^5 ng/hour) and maximum (6.52×10^5 ng/hour) values, respectively.

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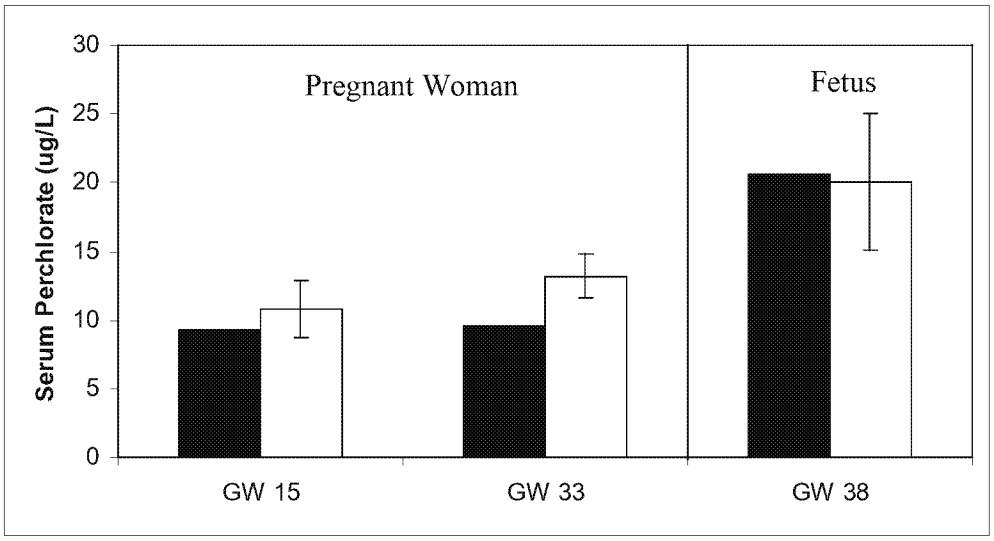

Figure 4-6. EPA-modified PBPK model predictions of perchlorate in the pregnant woman at GWs 15 and 33 and in the fetus at birth (GW 38).

Model predictions (dark bars) shown with measured perchlorate (light bars ± 1 SD) following exposure to 114 ppm perchlorate in drinking water. Similar simulations were originally shown in Clewell et al. (2007, Figure 10).

4.1.1.3.3. ***Lactating Woman and Neonate.*** Model predictions obtained by using the PBPK models as modified by EPA were compared with published radioiodide and perchlorate data previously simulated by Clewell et al. (2007) and are shown below in Figures 4-7 and 4-8.

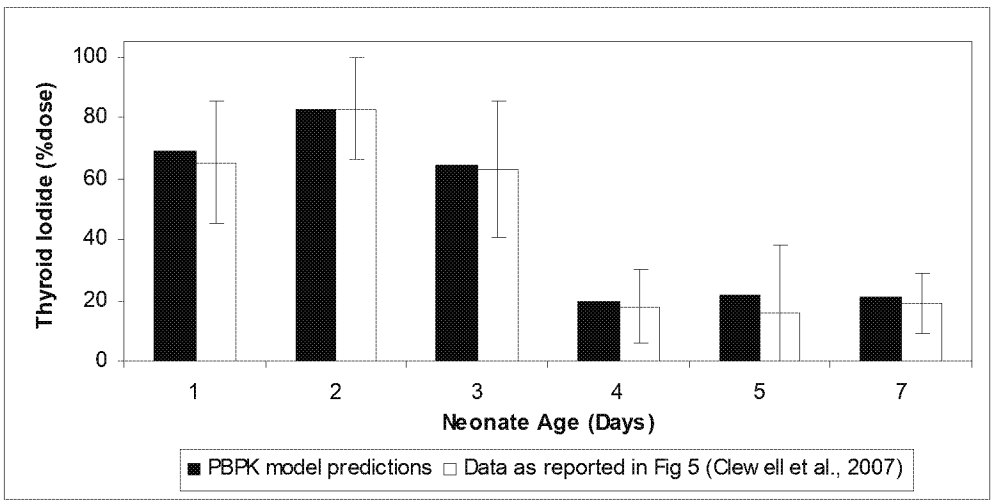

Figure 4-7. EPA-modified PBPK model predictions of neonatal thyroid radioiodide uptake compared with data ± SD as reported in Clewell et al. (2007, Figure 5).

Twenty-four hour thyroid iodide uptake (as % dose) following i.v. dose to the neonate at 1, 2, 3, 4, 5, and 7 days following birth.

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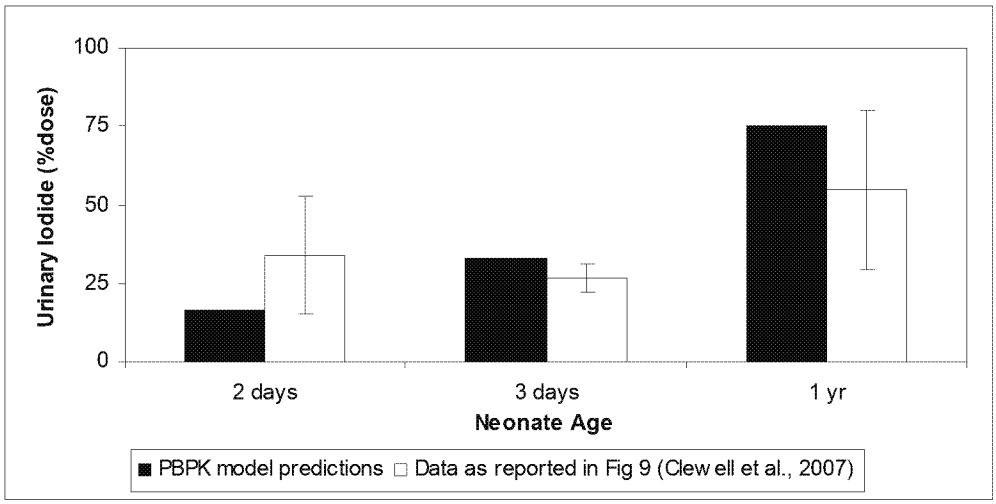

Figure 4-8. EPA-modified PBPK model predictions of neonatal urinary radioiodide excretion compared with data ± SD as reported in Clewell et al. (2007, Figure 9).

Twenty-four hour urinary excretion (as % dose) following i.v. dose to the neonate at 2 days, 3 days, and 1 year following birth.

4.2. LIFE STAGE RELATIVE RESPONSE ANALYSIS

For this document and analysis, *sensitivity* is defined as the predicted response in percent RAIU inhibition 24 hours after iodide i.v. injection for an average individual within a specific subgroup (e.g., bottle-fed infants) relative to the predicted response in percent RAIU inhibition for an average, nonpregnant adult, where response is the percent RAIU inhibition 24 hours after iodide i.v. injection.

The PBPK models published by Merrill et al. (2005) and Clewell et al. (2007) were modified as described above and in the appendices and used to estimate the predicted percent RAIU inhibition for the average adult and different subgroups, including potentially sensitive subgroups. These estimates were made assuming a dose equal to the POD of 7 μg/kg-day, which was identified by NRC (2005) as a NOEL for the derivation of the RfD and adopted by EPA. The POD was the level at which no significant inhibition of RAIU was observed in a group of healthy adult volunteers. Table 4-3, column 3, shows the PBPK model predictions of percent inhibition of RAIU at the 7 μg/kg-day dose rate. The relative sensitivity of different subgroups was determined by comparing the percent RAIU inhibition of each subgroup to the percent RAIU inhibition for an average adult at a dose equal to the POD (Table 4-3, column 4).

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Table 4-3. Model-predicted RAIU inhibition and relative sensitivity of different subgroups compared with the average adult at a dose equal to the POD based on EPA's modified PBPK models

Population or life stage	BW (kg)[a]	RAIU inhibition at the POD (7 µg/kg-day)	Relative sensitivity vs. average adult at the POD
Average adult	70	1.6%	1
Woman (child-bearing age)	68	3.0% [b]	1.8
GW 13	Mother: 69	6.3%[c]	3.8
GW 20	Mother: 71	6.3% [c]	3.8
GW 40	Mother: 79	6.1% [c]	3.7
	Fetus: 3.5	11% [c]	6.7
Mother and breast-fed infant (7 days)	Mother: 74	2.1% [d]	1.3
	Infant: 3.6	5.4%[d, e, f]	3.3
Mother and breast-fed infant (30 days)	Mother: 73	2.0% [d]	1.2
	Infant: 4.2	4.4%[d, e, f]	2.7
Mother and breast-fed infant (60 days)	Mother: 72	2.0% [d]	1.2
	Infant: 5.0	4.2%[d, e, f]	2.5
Bottle-fed infant (7 days)	Infant: 3.6	4.3%[e]	2.6
Bottle-fed infant (30 days)	Infant: 4.2	2.9%[e]	1.8
Bottle-fed infant (60 days)	Infant: 5.0	2.5%[e]	1.5
Child (0.97 years)[g]	Child: 10	1.7%[h]	1.1
Child (2 years)	Child: 14	1.7% [h]	1.1

[a]The BW (70 kg) for the average adult is the default weight used by the Office of Water. All other BWs are generated by the model.

[b]Results were obtained by using modified code in which fetal and placental compartments were removed from the code for pregnancy. Maternal BW was held at the value defined at the start of pregnancy (BW = 67.77 kg), and the "average adult" urinary clearance values as published by Merrill et al. (2005) were used.

[c]Results are based on using the maternal urinary clearance as published in Clewell et al. (2007), which is equal to about half of the average adult clearance.

[d]Results are based on setting the maternal clearance rates of both perchlorate and iodide during lactation equal to the rate of the average adult. Clewell et al. (2007) used an iodide clearance rate equal to that of an average adult but a perchlorate rate only half that of the average adult.

[e]Percent RAIU inhibition given for the infant is provided based on a value of urinary clearance scaled from the adult by $BW^{2/3}$ to approximate surface-area scaling and then multiplied by a rising fraction vs. age based on data (DeWoskin and Thompson, 2008) to reflect the reduction in GFRs (see section 3.1 and Appendix B.3 for further details). Clewell et al. (2007) scaled urinary clearance by $BW^{0.75}$ rather than adjusting based on GFR.

[f]These percent RAIU inhibition values are based on an internal dose to the breast-fed infant of 7 µg/kg-day, the same as for the other subgroups. Maternal dose rates lower than the POD are needed to provide 7 µg/kg-day to the infant (see Table 4-2, notes), as follows: 7 days, 2.7 µg/kg-day; 30 days, 3.0 µg/kg-day; 60 days, 3.6 µg/kg-day. These doses differ due to changes in BWs and other pharmacokinetic factors with age.

[g]Because Office of Water typically uses a 10 kg child as a default assumption for its health advisories, the model was run for a child at 0.97 years, the age at which the model-simulated BW for a child is 10 kg.

[h]Results were obtained by setting urinary clearance constants for the older child equal to the average adult (Merrill et al., 2005) and scaling by $BW^{1.0}$.

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EPA's model predictions may generally be considered central estimates for each subgroup (at the consumption levels modeled) that account for pharmacokinetic (PK) differences and do not take into account within-group variability in pharmacokinetics, uncertainty in model parameters and predictions, or population differences in pharmacodynamics (PD). Fetal simulations are only reported for the end of gestation (GW 40), since key fetal parameters are considered to be too uncertain for reliable use earlier in gestation and there are no data to support model predictions or parameters for earlier gestation. Note that results for the GW 40 fetus should not be assumed to also represent the sensitivity of the first or second trimester fetus, a life stage for which reliable estimates cannot be made. However, maternal parameters are considered to be more reliable, so maternal predictions are also shown for GWs 13 and 20.

In this analysis, urinary clearance was identified as a key parameter (i.e., model predictions were highly sensitive to the value used for this variable). Given the range of uncertainty about urinary clearance during pregnancy and early infancy, the most "sensitive" (lowest) value was selected from a range of potential values that were identified, while during lactation (breast-feeding woman), the middle option (2) was selected. See section 3.1, above, for details. However, a full population analysis of urinary clearance was *not* conducted, and given that variability in other PK parameters was not addressed, these estimates should not be considered a true upper confidence bound on RAIU inhibition.

When compared to the average adult, the fetus was identified by EPA's analysis as the most sensitive subgroup with respect to percent RAIU inhibition at a dose equal to the POD. This finding is consistent with prior PBPK modeling analyses by Clewell et al. (2007). The predicted percent RAIU inhibition is approximately 6.7-fold higher for the fetus at GW 40 than for the average adult. (Simulations at earlier GWs indicate that the fetus is more sensitive than the adult throughout pregnancy but are considered too quantitatively uncertain to assign exact relative sensitivities.) The same analysis shows that the predicted percent RAIU inhibition is approximately one- to threefold higher for the breast-fed and bottle-fed infant (7–60 days) than for the average adult and is approximately equal for the 1- to 2-year-old child compared to the average adult.

To the extent that predictions of percent RAIU inhibition for the different subgroups are close to the average adult, this provides greater confidence in applying the existing RfD for these subgroups, which is based on an uncertainty factor of 10 to account for intraspecies variability. While the difference estimated for fetuses is larger than for other groups, EPA's analyses indicate that, due to differences in exposure, fetuses whose mothers drink water containing perchlorate would be predicted to have somewhat lower predicted RAIU inhibition than would other sensitive subgroups.

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4.3. LIFE STAGE COMPARISON FOR THREE DRINKING WATER CONCENTRATIONS

EPA evaluated the percent RAIU inhibition at various water concentrations, with and without perchlorate intake from food sources, for the different life stages. EPA-adjusted models based on Clewell et al. (2007), as described earlier, were used to simulate three drinking water concentrations (15, 20, 24.5 ppb) (Table 4-5). Available literature was used to estimate water intake rates for the different life stages as well as the dietary contribution to the average daily dose of perchlorate, as described below.

The water intake rates used for the average adult, nonpregnant and pregnant woman are based on normalized 90th percentile values for total (direct and indirect) consumers-only water intake multiplied by the age- or GW-dependent BW. (Direct water consumption is that used for drinking; indirect consumption is that used for food preparation and therefore ingested with food.) EPA selected the 90th percentile drinking water intake value for most of the subpopulations evaluated in this report in order to explore the potential effects of high-end exposure to perchlorate from public water systems. The approach is consistent with the *Guidelines for Exposure Assessment* (U.S. EPA, 1992) and with EPA policies and procedures for deriving health-based drinking water values, including MCLGs, HA values, and HRLs. EPA acknowledges that modeling a complete distribution of water ingestion would be more informative; however, due to time and data constraints, EPA selected a high-end water intake estimate as the most appropriate means to explore the potential effects of drinking water exposure on subpopulations. EPA selected community water ingestion for the analysis to characterize the high-end exposure to perchlorate from public water systems (as opposed to bottled water or private well water, which is captured in the total water ingestion). For this assessment, in support of EPA's evaluation needs under SDWA, EPA's interest in the impact of perchlorate from direct and indirect community water consumption is considered. EPA further notes that less than 1% of public water systems reported detecting perchlorate at concentrations greater than 15 μg/L. Therefore, by evaluating populations consuming the 90th percentile of drinking water with concentrations of perchlorate at 15, 20, and 24.5 μg/L, EPA is providing a realistic high-end exposure estimate.

The water intake rates used to estimate daily perchlorate exposure from drinking water were 0.032 L/kg-day (Kahn and Stralka, 2009; U.S. EPA, 2004) for the average adult and nonpregnant woman and 0.033 L/kg-day for the pregnant woman (U.S. EPA, 2004). However, a constant water intake rate (2.96 L/day, 90th percentile, consumers only [U.S. EPA, 2004]) for the lactating mother was used since her BW is expected to decrease during the weeks following pregnancy, while demands of breast-feeding increase. For the 6- to 12-month-old and 1- to 2-year-old children, the water intake rates of 0.112 L/kg-day and 0.056 L/kg-day, respectively, were set based on 90th percentile values for direct and indirect water consumers-only intake (from Kahn and Stralka [2009, Table 4]). Additionally, to calculate L/day for these age groups,

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the corresponding age group mean BWs obtained from National Health and Nutrition Examination Survey 1999–2006 were used: 9.2 kg for 6- to 12-month-old children and 11.4 kg for 1- to 2-year-old children. Using the PBPK model-predicted BW from growth equations, this approach resulted in model predictions for a 9.6-month-old child and a 1.3-year-old child. A different approach was used to estimate the breast- and bottle-fed infant breast milk and formula intake rates, respectively (see sections 3.3.1 and 3.3.2 for details regarding these intake rates).

The dietary doses of perchlorate used correspond to the midpoint of the range of lower- and upper-bound average perchlorate dietary intakes for each subgroup, as identified from the U.S. Food and Drug Administration (FDA) Total Diet Study (TDS) (Murray et al., 2008), except for the breast- and bottle-fed infants. The breast-fed infants are assumed to have no direct exposure via food or water. The estimates for breast-fed infants in Table 4-5 result from the combined food and water dose to the mother providing breast milk to the infant.

The bottle-fed infant TDS was derived from the infant formula concentrations of perchlorate reported in the FDA TDS data available online (U.S. FDA, 2008a). EPA selected the FDA TDS data to represent the dietary intake of perchlorate because the TDS is the best available nationally representative estimate of dietary exposure to perchlorate for the majority of the sensitive subpopulations of concern, including infants and children. The data gathered for 2005–2006 resulted in detection of perchlorate in 8 of the 12 samples (soy- and milk-based formulas) with a detected concentration mean of 1.875 ppb (limit of detection [LOD] 1.0 ppb). Using 0.5 ppb (half the LOD) for the samples in which perchlorate was not detected, the average is 1.42 ppb. Each of the 12 values represents a composite sample, based on samples collected four times a year in four geographical locations for 5-week periods and in three cities in each region. The samples reported by the FDA are shown in Table 4-4, along with the market basket averages and the overall average calculated as described above.

Table 4-4. The FDA TDS perchlorate data in infant formula for 2005–2006

TDS food #	Food description	Perchlorate level (ppb)			
		Market basket 1	Market basket 2	Market basket 3	Market basket 4
202	Infant formula, milk, high iron	ND	2.5	2	2
203	Infant formula, milk, low iron	1.2	ND	3.6	2.1
309	Infant formula, soy	ND	ND	0.8[a]	0.8[a]
	Market basket average[b]	0.73	1.17	2.13	1.63
	Overall average	1.42			

[a]Estimated value; result was below level of quantitation but above LOD.
[b]Non-detects (NDs) were averaged at one-half the LOD of 1 ppb.

Source: U.S. FDA (2008a)

In addition to the FDA TDS data, EPA also considered the results of a study by Pearce et al. (2007). Samples of 17 brands of prepared liquid formula analyzed by Pearce et al. (2007)

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averaged 1.45 ppb perchlorate, consistent with the FDA TDS information. In addition to calculating the bottle-fed infant percent RAIU inhibition for 1.42 ppb contribution from infant formula (Table 4-5), the bottle-fed infant model sensitivity to a change in TDS was tested by using 1 ppb and 3.6 ppb. A decrease from 1.42 to 1 ppb resulted in a change of –0.05 and –0.03% RAIU inhibition for the 7- and 60-day-old bottle-fed infants, respectively. Conversely, an increase from 1.42 to 3.6 ppb resulted in a change of +0.28% and +0.17% RAIU inhibition for the 7- and 60-day old bottle-fed infants, respectively.

Assuming a 90th percentile water ingestion rate of 0.033 L/kg-day and perchlorate intake from food consumption of 0.1 μg/kg-day and using the Clewell et al. (2007) PBPK model-fitted BW, the pregnant woman's dose of perchlorate was estimated to not exceed the RfD if she consumed less than 15 μg/L of perchlorate in drinking water.

There are uncertainties associated with this modeling, as there are for any modeling effort. For example, this analysis does not take into account within-group variability in PK, uncertainty in model parameters and predictions, or population differences in PD. Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation. These models were not designed to account for whether the pregnant woman is hypothyroid or iodine deficient. Model predictions of doses in the various subgroups apply to a subgroup average for typical, healthy individuals and effectively describe the RAIU inhibition relative to that same individual as his/her own control. Some members of a group would be expected to have RAIU inhibition greater than indicated in Table 4-5 for a particular perchlorate concentration, while others would have lesser inhibition. This would be expected for fetuses as well as for other subgroups. Likewise, the model does not allow for predictions of how RAIU inhibition, or the impact of that inhibition, might change with dietary iodide status (i.e., in an iodide deficient individual or one with more than sufficient dietary iodide).

There is also some uncertainty regarding the water intake rates, particularly for infants. EPA described water intake by infants as a smooth function fit to the 90th percentile community water-consumers' intake rate data (intake per unit BW) of Kahn and Stralka (2009), which is then multiplied by the age-dependent BW to account for the changes occurring over the first weeks of life. This resulted in an estimated 90th percentile water intake rate of 0.84 L/day for the 7-day-old bottle-fed infant and was used by EPA in PBPK model simulations. General information on water and formula intake for 7-day-old infants is also available in guidelines for healthy growth and nutrition of the American Academy of Pediatrics (AAP) (Hagan et al., 2008). The values estimated by using the guidelines from the AAP (0.126 L/kg-day, assuming 80% is the percent water used in preparation of formula) for 7-day-old infants are close to the mean consumers-only intake rate for the 1- to 30-day-old infants from the Kahn and Stralka (2009) study (0.137 L/kg-day; n = 40).

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Table 4-5. Predicted percent RAIU inhibition and corresponding perchlorate intake (µg/kg-day) at three different water concentrations with and without food intake

	Body weight (kg)[a]	90th Percentile water intake (L/day)[b]	% RAIU inhibition Perchlorate intake (µg/kg-day) Water only			TDS food (µg/kg-day)[c]	% RAIU inhibition Perchlorate intake (µg/kg-day) Food + water		
			15 µg/L	20 µg/L	24.5 µg/L		Food + 15 µg/L	Food + 20 µg/L	Food + 24.5 µg/L
Average adult	**70**	**2.24**	0.11	0.15	0.18	**0.1**	0.13	0.17	0.20
µg/kg-day			0.48	0.64	0.78		0.58	0.74	0.88
Nonpregnant woman	**66**	**2.11**	0.21	0.27	0.34	**0.1**	0.25	0.32	0.38
µg/kg-day			0.48	0.64	0.78		0.58	0.74	0.88
Pregnant woman									
Mother—GW 13	*69*	**2.18**	0.47	0.63	0.77	**0.1**	0.57	0.73	0.87
µg/kg-day			0.50	0.66	0.81		0.60	0.76	0.91
Mother—GW 20	*71*	**2.34**	0.46	0.62	0.76	**0.1**	0.56	0.72	0.85
µg/kg-day			0.50	0.66	0.81		0.60	0.76	0.91
Mother—GW 40	*78*	**2.57**	0.45	0.60	0.74	**0.1**	0.54	0.69	0.83
µg/kg-day			0.50	0.66	0.81		0.60	0.76	0.91
Fetus—GW 40	*3.5*	–	0.89	1.2	1.4		1.1	1.4	1.6
			–	–	–		–	–	–
Breast-fed infant									
Mother—7 d	*74*	**2.96**	0.18	0.24	0.30	**0.1**	0.21	0.27	0.33
µg/kg-day			0.60	0.80	0.98		0.70	0.90	1.1
Infant—7 d	*3.6*	**0.60**[d]	1.1	1.5	1.8	–[d]	1.3	1.7	2.0
µg/kg-day			1.6	2.1	2.6		1.8	2.4	2.8
Mother—60 d	*72*	**2.96**	0.18	0.24	0.29	**0.1**	0.21	0.26	0.32
µg/kg-day			0.61	0.82	1.0		0.71	0.92	1.1
Infant—60 d	*5*	**0.68**[d]	0.75	1.0	1.2	–[d]	0.87	1.1	1.3
µg/kg-day			1.2	1.6	2.0		1.4	1.8	2.2
Bottle-fed infant									
Infant—7 d	*3.6*	**0.84**[e]	2.0	2.6	3.2	**1.42 ∝g/L**	2.2	2.8	3.4
µg/kg-day			3.5	4.7	5.8		3.9	5.0	6.1
Infant—60 d	*5*	**1.14**[e]	1.2	1.6	2.0	**1.42 ∝g/L**	1.3	1.7	2.1
µg/kg-day			3.4	4.6	5.6		3.7	4.9	5.9
Older child									
6–12 mo[f]	*9.2*	**1.03**	0.42	0.56	0.69	**0.275**	0.49	0.63	0.75
µg/kg-day			1.68	2.24	2.74		1.96	2.52	3.02
1–2 yr[f]	*11.4*	**0.64**	0.21	0.28	0.35	**0.37**	0.31	0.38	0.44
µg/kg-day			0.84	1.12	1.37		1.21	1.49	1.74

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[a]Calculations for a 70 kg average adult are shown, while the BW for the nonpregnant woman is from U.S. EPA (2004, based on CSFII 94-96, 98), and BWs for the child are mean values from Kahn and Stralka (2009). BWs in italics are predicted weights (functions of age or GW), using growth equations from Gentry et al. (2002) as implemented in the PBPK models (Clewell et al., 2007) (nonpregnant value is BW at day 0 of gestation).

[b]Water intake levels for adults other than the lactating mother are based on normalized 90th percentile values for total water intake (direct and indirect) multiplied by the age- or GW-dependent BW as follows: 32 mL/kg-day for average adult and nonpregnant woman; 33 mL/kg-day for the pregnant woman. A fixed ingestion rate was used for the lactating mother because, while her BW is expected to drop during the weeks following the end of pregnancy, the demands of breast-feeding will be increasing. Values are from Kahn and Stralka (2009), with the exception of the values for women, which come from U.S. EPA (2004).

[c]The dietary values used correspond to the midpoint of the range of lower- and upper-bound average perchlorate levels for each subgroup, as identified from the FDA TDS in Murray et al. (2008), except for the bottle-fed infant. EPA used 1.42 μg/L as the concentration of perchlorate in infant formula. This is based on an the average of available FDA TDS data (U.S. FDA, 2008a), with ½ LOD included in the average for the samples in which perchlorate was not detected.

[d]The breast-fed infants are assumed to have no direct exposure via food or water. The prediction for breast-fed infants in this table results from the dose from both food and water to the mother providing breast milk to the infant. Breast-fed infant "water intake" is the breast milk ingestion rate obtained from the age-dependent Hill function fit to the breast milk ingestion data (L/kg-day) from Arcus-Arth et al. (2005), as shown in Figure 3-1. Urinary clearance rates for the lactating woman equal to that of the average adult were used, consistent with data presented in Delange (2004).

[e]For the bottle-fed infant, normalized total water intake (direct and indirect, L/kg-day) was described as a smooth function of infant age, fit to the results from Kahn and Stralka (2009) and multiplied by BW (age). The FDA has suggested an alternate approach, using the caloric intake requirement of a 7-day-old infant as the basis for calculating consumption (U.S. FDA, 2008b). This would likely yield a lower estimate of intake than the 0.84 L/day that EPA used in the model.

[f]For the 6- to 12-month-old and 1- to 2-year-old children, EPA set the water ingestion based on published exposure tables and selected the age at which the model-predicted BW matched the exposure-table mean. This approach resulted in model predictions for 0.796-year-olds (to represent 6- to 12-month-old children) and 1.285-year-olds (to represent 1- to 2-year-old children).

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5. OTHER SUSCEPTIBLE SUBGROUPS, MODEL UNCERTAINTY, AND DATA NEEDS

5.1. OTHER SUSCEPTIBLE SUBGROUPS

This analysis focused on the inhibition of thyroid radioiodide uptake by perchlorate on the average adult, nonpregnant woman, lactating woman, breast-fed neonate, bottle-fed neonate, and older child. The individuals in each of these categories were considered to be average, euthyroid individuals. Iodine deficiency, hypothyroidism, and other thyroid diseases were not considered. Additionally, effects of perchlorate in individuals also exposed to other iodide uptake inhibitors (e.g., thiocyanate, nitrate) were not evaluated.

The PBPK models developed by Merrill et al. (2005) and Clewell et al. (2007) were not developed with the goal of providing simulations of dietary iodide. The models accurately simulate trace amounts of radioiodide and inhibition of radioiodide uptake into the thyroid; however, the models are unable to handle the large mass flux of dietary iodide compared to radioiodide. Thus, in order to simulate iodine deficiency using these models, only qualitative estimates could be provided. In iodine deficiency or the hypothyroid state, the thyroid NIS is up-regulated (or stimulated) by thyroid-stimulating hormone. Thus, an arbitrary increase in V_{max} of NIS transport of iodide and perchlorate could give some qualitative indication of how the system might be affected (e.g., the degree to which NIS transport would change as well as the secretion, or loss of iodide, rate constant currently used in the model), but too many uncertainties exist for this information to be useful in this assessment. Thus, we do not have modeling predictions available for effects of perchlorate on iodide-deficient individuals.

5.2. MODEL UNCERTAINTIES AND LIMITATIONS

5.2.1. Model Uncertainties

Lack of data in various human life stages for model parameterization and validation is the cause for uncertainties associated with the use of the PBPK models developed by Merrill et al. (2005) and Clewell et al. (2007). In humans, the only data available for validation of thyroid percent RAIU inhibition model predictions are for the average adult human and were used in Merrill et al. (2005).

In the absence of thyroid percent RAIU inhibition data, other data sets have been used to demonstrate the ability of the models to predict radioiodide and perchlorate kinetics in various life stages. For the evaluation of their model, Clewell et al. (2007) used such data, the majority of which were collected in the 1950s and 1960s. These "validation" exercises are valuable in that they provide confidence that the models are predicting perchlorate and radioiodide distribution and elimination. In the absence of PBPK models, it would be necessary to rely on external dose as the estimate of maternal, fetal, and neonatal exposure. However, since

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perchlorate kinetics are governed by active transport as well as passive diffusion, the use of external dose does not provide a reliable estimate of internal dose.

The PBPK model parameters utilized by Clewell et al. (2007) were primarily derived by using a parallelogram approach, such that the relationship between model parameters for various life stages in the rat is similar in humans. The data available for validation of these parameters were minimal, especially in the developing fetus and neonate. Thus, confidence in these model predictions is less than in the average adult. But given the fact that these models are able to predict some data on the distribution of radioiodide in the fetus (see Clewell et al. [2007], Figure 7 and Table 3), serum perchlorate in the fetus/neonate at birth (see Clewell et al. [2007], Figure 10), and urinary iodide in the neonate (see Clewell et al. [2007], Figure 9), this provides a "medium" level of confidence in these model predictions.

Some model parameters are more certain than others. For instance, the NIS affinity constant for iodide and perchlorate has more substantial laboratory data than the estimates for urinary clearance and is known to be highly conserved (has little genetic variation) among humans. For this reason, a range of urinary clearance estimates were tested by EPA. Data needs that would help reduce model uncertainties are discussed further in section 5.3.

5.2.2. Model Limitations

Several limitations of the PBPK models are evident for evaluation of health effects of perchlorate. First, the PBPK models developed by Clewell et al. (2007) and Merrill et al. (2005) were not developed with the goal of describing dietary intake of iodide nor are they capable of such simulations because the parameters are not calibrated to handle such a large mass flux of iodide. Furthermore, these models were developed to predict percent inhibition of thyroid radioiodide uptake (percent RAIU inhibition) and were not elaborated on to include thyroid hormones and thyroid axis regulation. Thus, a qualitative evaluation of what effect perchlorate may have on RAIU inhibition in a hypothyroid (up-regulated NIS, increased NIS V_{max}) may be tested, but this has little importance because it cannot be directly compared with data. There are likely many other changes in iodide kinetics and thyroidal iodide processing in hypothyroid and other thyroid disease states that give a qualitative analysis little relevance.

The models are also not formulated to predict the combined inhibition of radioiodide uptake jointly when an individual is exposed to a mixture of perchlorate and other iodide uptake inhibitors (e.g., thiocyanate and nitrate). It should be noted, however, that perchlorate's potency as an inhibitor of radioiodide uptake at the NIS is 15 and 240 times greater than that of thiocyanate and nitrate, respectively (Tonacchera et al., 2004). It is the combination of potency and the relative blood concentration of these anions that ultimately determines the impact of total exposure on iodide uptake.

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5.3. DATA NEEDS

There are significant research needs that would contribute to the understanding of physiological processes pertaining to perchlorate and iodine and thereby reduce model uncertainty. Additional research could also provide the needed data for expansion of the PBPK models to include interaction with other iodide uptake inhibitors.

First, a detailed evaluation of the mechanisms of perchlorate renal clearance, including the effect of perchlorate on the clearance of NIS substrates, and perchlorate-induced perturbations in the thyroid axis and perchlorate inhibition of NIS are needed. Additional data on renal/urinary clearance of anions and environmental pollutants in various life stages, especially during pregnancy, post partum, and in neonates, are also needed. Furthermore, additional information to characterize perchlorate exposure to neonates is desired (i.e., measurements of perchlorate in non-composited baby formula samples and samples of powdered formula reconstituted with perchlorate-free water).

To further the understanding of effects of perchlorate in individuals exposed to other iodide uptake inhibitors, such as thiocyanate and nitrate, investigations of the toxicity of these compounds in the presence and absence of perchlorate, including effects on iodide uptake and the thyroid axis, would be useful. Biomonitoring of perchlorate, iodide, thiocyanate, and thyroid hormones during and after pregnancy and during lactation in smoking and nonsmoking women could provide information to better characterize co-exposure effects. In these instances blood levels and urine levels of compounds should be collected simultaneously, so that the relationship of blood levels and urinary excretion can be directly evaluated.

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6. SUMMARY AND CONCLUSIONS

Detailed examination of Clewell et al. (2007) determined that the model structure is appropriate for predicting percent inhibition of thyroidal RAIU following perchlorate exposure. While some coding errors were found, correction of these led to only minor changes in the NIS inhibition prediction in most cases. Beyond the issue of coding errors, a number of concerns and questions were raised regarding choices of parameter values in the models for each life stage. However, discussions with the authors of Clewell et al. (2007) about the technical basis for some of the parameter values clarified most such issues. Several issues with model choices made by the authors have also been noted and tested but found to not have marked impacts on model predictions (e.g., the equation and scaling used for binding of perchlorate and iodide to blood proteins, as described above). In cases that represent differences in scientific judgment rather than coding errors (some noted in Appendix A) and that result in minimal changes to the results, the model code has been left as is. The existing model structure has previously been peer reviewed; thus, it was concluded that the most expedient course was to not make these changes because of their minimal impact.

A few adjustments to the model components and procedures were made if it was determined that they could have more substantive impacts on the results. For example, the arrangement of terms in the equations describing transport in blood (mixing of venous blood streams and arterial blood compartment) was giving rise to numerical instabilities in the computer implementation. While the software used to solve the model appeared to be robust enough to handle this instability, such that there were minimal changes in model predictions when the equations were adjusted to remove them, it was deemed appropriate and better to use the modified code without instabilities.

Use of more accurate values for the rate of urinary clearance in neonates led to the greatest changes in predicted levels of NIS inhibition relative to those provided by Clewell et al. (2007). A few adjustments were also made to the lactation/breast-feeding model components and procedures, including the neonate's rate of milk ingestion. Overall, however, while the quantitative outputs of the PBPK model as modified by EPA differ from those published in Clewell et al. (2007) (see Table 4-1), EPA evaluation determined that, with modifications as described herein, Clewell et al. (2007) is acceptable to calculate the life stage differences in the degree of NIS inhibition of thyroidal radioiodide uptake at a given level of perchlorate exposure.

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APPENDIX A:
DESCRIPTION OF MODEL CODE ISSUES AND RESOLUTION

Computer code (acsl language, .csl and .cmd files) were provided by the authors (R.A. Clewell and E.A. Merrill) for the average adult (human10.csl [Merrill et al., 2005]), pregnant woman and fetus (HPregF.csl [Clewell et al., 2007]), lactating woman and breast-fed infant (HLactF.csl [Clewell et al., 2007]), and older child (HKidF.csl [Clewell et al., 2007]). Descriptions of specific issues and discrepancies identified in the code or among the code and model descriptions in the published papers follow, along with the resolutions. At the end of this appendix is a brief "impact of changes" listing that shows the impact of each change or set of changes on model predictions of inhibition of radioiodide uptake given exposure at the POD (7 μg/kg-day) and illustrates the quantitative results of these corrections.

A.1. Perchlorate Inhibition of Iodide Transport

During the review of the acsl CSL code provided by the authors for the average adult (human10.csl [Merrill et al., 2005]), pregnant woman and fetus (HPregF.csl [Clewell et al., 2007]), lactating woman and breast-fed infant (HLactF.csl [Clewell et al., 2007]), and older child (HKidF.csl [Clewell et al., 2007]), several apparent discrepancies between the manuscript and the code were noted that were related to NIS and pendrin inhibition of iodide transport by perchlorate. Understanding of the biology of NIS, along with the statement "[i]nhibition of iodide uptake was included in the maternal, neonatal, and fetal thyroid follicle and colloid, GI contents, and skin, as well as the maternal placenta, mammary gland, and milk, based on various literature sources showing inhibition in these tissues in laboratory animals and humans" in Clewell et al. (2007), led to the following concerns and actions:

1. Transport of iodide via NIS into GI contents was described with perchlorate inhibition in the human10.csl and HPregF.csl code for the average adult and pregnant woman and fetus but was not included in the code for lactating woman/infant and older child.

   Action: GI inhibition of NIS iodide transport by perchlorate was added to the model code for the older child and lactating woman/infant.

2. Transport of iodide via NIS into skin was described with perchlorate inhibition in the model code for the pregnant woman and fetus but was not included in the model code for the other life stages.

   Action: Skin inhibition of NIS iodide transport was added to model code for the average adult, older child, and lactating woman/infant.

   (a) Perchlorate inhibition of mammary iodide active transport was not included in the model code for both the pregnant woman and lactating woman. Also, iodide transport

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from mammary tissue to milk was not inhibited by perchlorate in the lactating woman model code.

(b) Of particular concern is that, qualitatively, a dual impact would be expected on the breast-fed infant, due to reductions in iodide received in breast milk, which the model code obtained from the authors did not predict due to the lack of an inhibition in the lactation/milk compartment.

Action: (a) Inhibition of iodide transport by perchlorate into the mammary tissue was added to the model code for the pregnant woman and lactating woman, and inhibition of iodide transport to milk was added in the lactating woman model code.

(b) The value of Km_Mkp of 10^6 ng/L in breast milk for the lactating woman was used. Iodide transfer to the infant was then simulated as the iodide concentration in breast milk times the suckling rate—a clearance term in the existing maternal model, by adding the term to the infant gastric juice compartment. This revised code was used to simulate ^{125}I levels in the infant thyroid at 24 hours after maternal ^{125}I-dosing (along with lactational transfer of perchlorate) to obtain the percent inhibition in the breast-fed infant.

A.2. Tissue and Blood Flow During Pregnancy/Lactation

While the adult woman PBPK code was adjusted by the model authors to reflect changes in body fat and mammary size during lactation, the equation used to adjust blood flow to the mammary gland in proportion to its size appeared to be in error, since the flow rate set by the equation at birth only reflected the portion of mammary volume resulting from the change (increase) during pregnancy, and not the initial (pre-pregnancy) volume to which that increase is added. The result is that the maternal mammary blood flow just after giving birth was less than the pre-pregnancy blood flow, even though the tissue volume was greater. The equation was corrected to reflect the total tissue volume at the end of pregnancy/birth.

A.3. Residual Milk Volume

Residual milk volume is the volume of milk available to but not consumed by the infant (Dewey et al., 1991) is the volume of milk that is retained in the mammary gland between feedings and was used in the PBPK models to determine the concentration of radioiodide and perchlorate in breast milk. It is unclear what reference was used by Clewell et al. (2007) to derive the residual milk volume (VMk = 0.632 L). The reference cited in the acsl computer code was Gentry et al. (2001); however, this reference was not included in the Clewell et al. (2007) manuscript. Furthermore, a search of PubMed and Google did not find a Gentry reference from 2001 or with the VMk value.

We evaluated Dewey et al. (1991), as suggested by an external reviewer, and agreed that it provided a value (0.109 L) for VMk that is appropriate for use in the lactation PBPK model.

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The VMk parameter was changed from 0.632 to 0.109 L, and the model sensitivity was tested. Model sensitivity to VMk was tested, and an 83% decrease from 0.632 to 0.109 L for VMk resulted in a less than 3% change in model calculated percent inhibition of radioiodide uptake. Thus, the model is not considered sensitive to this parameter, and the value for VMk was changed from 0.632 to 0.109 L.

A.4. Modification to Lactating Woman/Breast-Fed Infant Model to Provide for Bottle-Fed Infant Simulations

The model code for the lactating woman/breast-fed infant was modified slightly to provide model simulations of the bottle-fed infant. Specifically, for bottle-fed infant simulations, the perchlorate dose to the mother was set equal to zero, then either the existing direct-dosing rate (PDOSE_N) was set > 0 for fixed μg/kg-day rates and/or a fixed concentration was multiplied by the suckling rate (KTRANS in revised code) for fixed water concentrations. In those simulations the maternal code still ran but contributed nothing since the maternal dose was set to zero. An i.v. dose of iodide to the infant was simulated in order to calculate percent of thyroidal radioiodide uptake (percent RAIU) inhibition in the bottle-fed infant in contrast to the iodide dose being received via breast milk for the calculation of percent RAIU inhibition in the breast-fed infant.

A.5. Blood Flow vs. Plasma Flow

The models were constructed by using arterial plasma concentration coupled with whole blood (plasma plus red blood cells) flow rates to describe the amounts of iodide and perchlorate delivered to the tissues. Thus, the mass flow of free perchlorate (in plasma), to and from the tissue compartments, is nearly double what physiology indicates. Either the influx in all mass balance equations should correspond to the effective concentration in whole blood (i.e., [plasma_concentration]*[volume_of_plasma]/[volume_of_plasma + volume_of_red_blood_cells]) or the flow rate should correspond to plasma flows, since the red blood cell:plasma partition coefficient (PRBC_p) is not always equal to 1, and the chemical movement between plasma and red blood cells is diffusion limited.

The effect of using plasma flow vs. blood flow on the predictions of percent RAIU inhibition was found to be very small; however, the model was corrected to reflect appropriate physiology. Cardiac output (total blood flow) was adjusted to reflect plasma flow by multiplying by the plasma:whole blood volume ratio (≈ 0.557), thereby decreasing the flow to the tissues. This had a small impact on model output although within the experimental error for the average adult (at 7 μg/kg-day, it changed from 2.1% RAIU inhibition to 1.6%).

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A.6. Model Code Errors, Little to No Quantitative Impact on Model Predictions

In the binding equation for iodide in the blood for the pregnant woman, lactating woman, and older child models, the term for concentration of iodide in the arterial blood (Ca_i or Ca_ni) appeared twice in the denominator. This effectively reduced the K_m and V_{max} for blood binding by half, but had minimal effect on model predictions at the concentrations tested (within linear range of blood binding). The extra Ca_i term was removed in these models.

The perchlorate mass balance equation, used as a flag for computational errors, was corrected for perchlorate by adding the amount of perchlorate in the "deep" thyroid, ADT_p, to the total mass in tissue (TM_1p) equation. The iodide mass balance equation (BAL_i) was corrected by adding the amount bound in blood (ABND_i) to the total mass in blood (TM_2i) equation and changing QS to QF in the equation for the rate of change in fat tissue (RAF_i).

In the model code equation for the concentration of iodide in venous blood (CV_i) in the average adult model, blood binding of iodide had an addition sign (+) instead of multiplication (*) between the Km and the perchlorate inhibition term; i.e.,

Vmax_Bi*CA_i/[CA_i + Km_Bi + (1_+ Ca_p/Km_Bp)]

instead of

Vmax_Bi*CA_i/[CA_i + Km_Bi × (1_+ Ca_p/Km_Bp)]

EPA changed the + to a ×; this had minimal impact on model predictions. The blood binding equation (RAbnd_i) had the correct operator.

Additionally, blood binding of iodide and perchlorate are described slightly differently in the average adult model code (human 10.csl) and in the maternal and neonatal code (HlactF.csl). For perchlorate the rate of change of bound perchlorate is subtracted from the equation for the rate of change in the arterial plasma (RPLAS_p), which determines the concentration in arterial blood (Ca_p), and Ca_p is subsequently used in the Michaelis-Menten binding equation; however, for iodide, the rate of change of bound iodide is subtracted from the *venous* blood concentration (CV_i) equation and Ca_i is still used in the Michaelis-Menten binding equation. EPA notes that Ca_i and Cv_i are typically very close if not equal to one another. The term for iodide binding was therefore moved from the venous to the arterial blood equation. As was expected, this change had minimal impact on model predictions; however, making this change did seem to improve computation speed and stability.

The change in uterine weight was not included in the total maternal BW calculation in the original code used in Clewell et al. (2007). Including the increase in uterine weight in the maternal BW calculation increased maternal BW by approximately 3%, but this correction did not affect prediction of percent RAIU inhibition in the pregnant woman or fetus for the time points examined.

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A.7. Impacts of Various Changes on Model Predictions

Described below are differences between the percent RAIU inhibition predictions of the PBPK models as originally published/described by the authors and the percent RAIU inhibition predictions now obtained with the models. The differences are illustrated with model predictions at the POD of 7 μg/kg-day. The predictions of the models originally published/described are in the first sub-bullet (>) in each category, and the effects of EPA's changes are noted in the subsequent sub-bullets. In most cases, only those adjustments that resulted in relatively large changes were noted. For each of these life stages/populations, other technical corrections that are not described here and had only minimal effects were also made.

<u>Changes in percent RAIU inhibition predicted by the model with changes in code and parameters</u>

∞ Average (nonpregnant) adult—original model predictions assumed perchlorate in four equal doses at 4-hour intervals, corresponding to the Greer et al. (2002) study protocol:
- > 3.3%—original value from Table 2 (1st one, page # 8 at bottom), Mattie (2006)
- > 3.1%—assuming continuous/steady-state perchlorate exposure
- > 2.1%—adding inhibition of iodide transport in skin (correction)
- > 1.6%—flow to tissues adjusted from blood flow to plasma flow (correction)

∞ Pregnant woman:
- > 6.4%—original value from Table 2 (Mattie, 2006), GW 38
- > 6.3%—multiple small corrections (e.g., + inhibition in mammary gland), continuous exposure
- > 6.1%—maternal and fetal flow to tissues adjusted from blood flow to plasma flow (correction), GW 38—using original Clewell et al. (2007) clearance values

∞ Fetus (exposure is to mother, per total maternal BW):
- > 8.6%—original value from Table 2 (Mattie, 2006), GW 38
- > 7.6%—multiple small corrections, as above, GW 38
- > 9.9%—inhibition at GW 40
- > 11.0%—maternal and fetal flow to tissues adjusted from blood flow to plasma flow (correction) at GW 40—using original Clewell et al. (2007) clearance values

∞ Lactating woman—original model used four doses at 4-hour intervals:
- > 6.9%—original value, PND 30
- > 3.8%—adding inhibition of iodide transport in skin and breast milk (corrections)
- > 4.1%—assume continuous dosing/ingestion; other small changes (e.g., blood binding)
- > 2.0%—revised urinary clearance (increased from original), KTRANS equation changed to Hill function (revised lactation expression), PND 30
- > 1.8%—flow to tissues adjusted from blood flow to plasma flow (correction), PND 30
- > 2.0%—VMk constant changed from 0.632 to 0.109 L, PND 30

∞ Breast-fed neonate (exposure is to mother, 7.0 μg/kg maternal BW):
- > ≈7%—original value (interpolated from Table 1, Mattie [2006]), age 1 month
- > 11.6%—including inhibition of iodide transfer in breast milk and maternal skin; other fixes

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- 18.5%—revised (reduced) urinary clearance to scale as GFR vs. adult (Appendix B)
- 12.1%—age 7 days, KTRANS equation changed to Hill function (revised lactation expression)
- 12.1%—age 7 days, flow to tissues adjusted from blood flow to plasma flow (correction)
- 12.5%—age 7 days, VMk changed from 0.632 to 0.109 L

∞ Bottle-fed neonate (since dose-rate fixed, milk ingestion rate does not impact these):
- 1.3%—original value (interpolated from Table 1, Mattie [2006]), 1-month-old
- 1.2%—small corrections
- 3.0%—revised (reduced) urinary clearance to scale as GFR vs. adult (Appendix B)
- 4.1%—age 7 days
- 4.3%—age 7 days, flow to tissues adjusted from blood flow to plasma flow (correction),
- 2.9%—age 30 days, flow to tissues adjusted from blood flow to plasma flow (correction),

∞ Older child:
- 2.1%—original value Table 5 (Clewell et al., 2007); 7-year-old
- 1.7%—with inhibition in GI tract and skin, steady-state exposure simulation
- 2.0%—revised clearance for perchlorate (scale as $BW^{1.0}$, Appendix B), 7-year-old
- 1.9%—revised clearance, 2-year-old
- 1.9%—revised clearance, 1-year-old
- 1.7%—flow to tissues adjusted from blood flow to plasma flow (correction), 2-year-old
- 1.7%—flow to tissues adjusted from blood flow to plasma flow (correction), 1-year-old

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APPENDIX B:
EVALUATION OF URINARY CLEARANCE PARAMETERS

B.1. Overview

In the PBPK models of Merrill et al. (2005) and Clewell et al. (2007), the urinary clearance of perchlorate and iodide are described by using a common form of allometric scaling by BW raised to the ¾ power. The actual urinary clearance constant for an individual of a given BW is given as follows:

$$CLU_k = CLUC_k \times BW^{0.75} \qquad \text{(Eq. B1)}$$

where CLU_k has units of L/hour and "*k*" is either "P" for perchlorate or "I" for iodide.

Note 1: The tables in the papers identify the units of the CLUCs as L/hour-kg, but clearly this should be L/hour-$kg^{0.75}$ to be consistent with this mathematical formulation, which is how the CLU values are calculated in the computer code. This form of allometric scaling is commonly used in PBPK models and is generally considered appropriate for estimating changes with individual BWs. Also, the tables list $CLUC_P = 0.13$ (± 0.05 in Merrill et al. [2005]) and $CLUC_I = 0.11$ (Merrill et al., 2005) or 0.1 (Clewell et al., 2007). The values as set in the computational command (.cmd) file were 0.125 and 0.11 for perchlorate and iodide, respectively, so these values will be used below.

These values for $CLUC_k$ were determined from PK data in adult humans, so henceforth they will be identified as the "adult" values.

Note 2: The similar values of $CLUC_k$ for perchlorate and iodide suggest that these are handled similarly by the kidney, as would be expected given their similar charge and ionic/molecular diameter. As will be discussed below, there is evidence for re-uptake activity by the pendrin transporter for iodide in the kidney, though only significant at lower concentrations, and for perchlorate-iodide interactions in renal clearance. While this transporter appears to operate on both iodide and perchlorate, the V_{max} for iodide is significantly higher than for perchlorate, and other tissues where it is explicitly described in the models capture this differential activity. This difference between iodide and perchlorate transport, and the fact that it appears to have small impact at higher (test) iodide concentrations corresponds nicely with the small difference in adult $CLUC_k$ values: if ≈10% of iodide is actively resorbed, but a much smaller faction of perchlorate, such a difference would be predicted.

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The current model does not include active renal transport per se but describes renal excretion as follows:

$$rCLU_k = CLUC_k \times CVK_k \qquad \text{(Eq. B2)}$$

where CVK_k is the concentration of k in the venous blood exiting the kidney. Inclusion of active (saturable) transport would lead to a nonlinear formulation. The error from not including the active transport is considered to be within the realm of PK uncertainty and variability that is *not* included in the current model applications. So, a revision of the model to include it is not proposed. But in application of these results, the fact should be considered that not all of the interindividual variability and uncertainty in the perchlorate and iodide PK has been quantified.

Given that this linear formulation is accepted and the implicit suggestion that renal clearance is largely controlled by glomerular filtration and nonspecific fluid resorption, the expectation is that the relative clearance for iodide and perchlorate (i.e., CLU_I/CLU_P) should be constant across ages, BWs, and life stages. In EPA's evaluation for the child and average (nonpregnant, non-lactating) adult, this proportionality has been maintained.

Note 3: In Clewell et al. (2007) it is stated "The maternal urinary clearance value (*Cluci*) was set at 60% of the value in the non-pregnant human based on observed difference in the pregnant and male rat models (Clewell et al., 2003b; Merrill et al., 2003)." In fact both $CLUC_I$ and $CLUC_P$ were set to 0.05 in the pregnant woman (both reduced by about the same proportion), but, in the lactating woman, only $CLUC_p$ was so reduced while $CLUC_I$ was not. These maternal lactation values go against the argument given above that the proportionality should be maintained, but EPA chose to use the maternal values as set. It is likely worthwhile to evaluate these maternal values in light of the generally higher urinary excretion seen in pregnant/lactating women, but alteration of these clearance constants would require refitting of other parameters, and so EPA chose not to conduct that specific evaluation.

B.2. Urinary Clearance in Adults (Outside of Pregnancy/Lactation)

With the use of the calculations as indicated above, the clearance rate from the Merrill et al. (2005) model for average adults is $CLU_P = CLUC_P \times 70^{0.75} = 3.025$ L/hour = 50.4 mL/minute. The average GFR in adults is 125 mL/minute = 7.5 L/hour, so CLU_P/GFR = 40%. For iodide the values are 2.662 L/hour or 44.3 mL/minute, 35% of GFR.

For comparison, Gardner et al. (1988) examined the effects of iodide supplementation in men, and a plot and regression of their data (urinary clearance vs. blood concentrations) is shown in Figure B-1. The slope of the regression line, 49.9 mL/minute, is quite close to the clearance value used by Merrill et al. (2005), and, if the intercept is forced to zero, the slope reduces to 40.5 mL/minute, bracketing that value. However, as indicated by the dashed line, drawn for illustration, the clearance must be considerably reduced at lower concentrations, assuming that

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clearance does not become zero until the blood concentration also drops to zero. (The slope of the dashed line is about 10 mL/minute.)

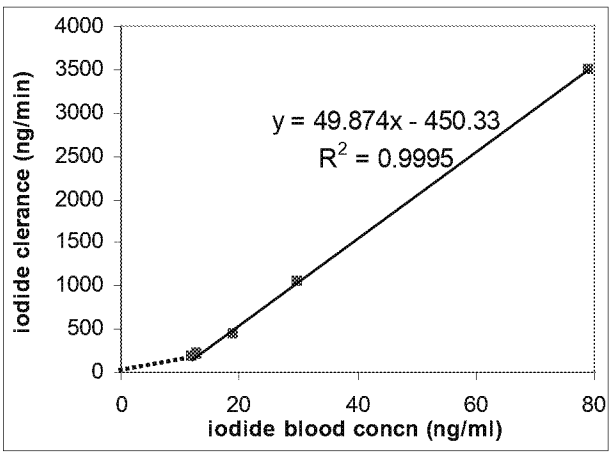

Figure B-1. Iodide clearance vs. blood levels in men, from Gardner et al. (1988).

What these data and regression indicates is that there is a nonlinearity in clearance at low levels, which could well be due to active reabsorption that becomes saturated at higher concentrations. The presence of the pendrin transporter in the kidney is noted in the review of Soleimani and Xu (2006).

While EPA does not propose changing the model to explicitly include active transport in the kidney, thereby describing this nonlinearity in excretion, it is noted here as a source of uncertainty or variability in model predictions: clearance values obtained at high concentrations (clinical experiments) might not be completely predictive of values at lower concentrations.

The presence of a transporter (more) active towards iodide, could explain the slightly lower clearance of iodide vs. perchlorate in the adult. It is assumed that this transporter acts at a similar proportion of activity in all life stages and hence that the ratio of perchlorate:iodide transport is approximately constant. Likewise, it is assumed (as one means of estimation) that the clearance rates remain at about 40 and 35% of GFR for perchlorate and iodide, respectively.

B.3. Urinary Clearance in the Neonate

Note 4: The analysis here focuses on clearance of perchlorate, but, as indicated above, iodide clearance was always changed in parallel to maintain the ratio of 0.11/0.125. Furthermore, for each alternate value of CLU_k evaluated, the V_{max} for NIS-mediated uptake of both iodide and perchlorate in the follicle (from blood to follicle tissue) was adjusted to maintain model fits to RAIU data (available for infants and other life stages in the absence of perchlorate).

Data from Guignard et al. (1975) on GFR in infants (age 1–25 days) with a linear regression are shown in Figure B-2. As a basis for comparison, EPA will consider the clearance

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of a 3.6 kg child, the (average) weight predicted by the model to occur at 7 days of age. Based on the regression shown below, GFR at that age/BW is 3.557 mL/minute or 0.21 L/hour. As implemented in Clewell et al. (2007), the clearance of perchlorate is predicted to be $CLU_P = 0.125 \times 3.6^{0.75} = 0.33$ L/hour. Clearly this value of CLU_P does not fit with the assumptions on clearance/GFR stated above; the only way in which clearance could be higher than GFR is if there is active excretion of iodide with no or substantially reduced resorption. EPA is aware of no data on renal transporters during infancy to suggest the level and pattern of expression changes required to bring about such an effect. If, instead, an assumption is made that perchlorate clearance was 40% of GFR, as it is in the adult, the value obtained at 3.6 kg BW would be 0.085 L/hour, almost four times lower than the default extrapolation.

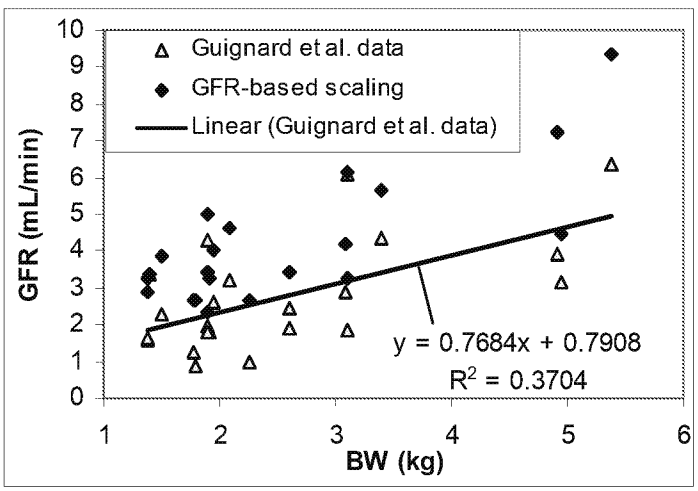

Figure B-2. GFR vs. BW in infants (Guignard et al., 1975).

GFR-based scaling uses equation B3 (with total adult GFR of 125 mL/minute vs. 3.025 L/hour perchlorate clearance) with individual age (day) and BW values from Guignard et al. (1975).

Since the intent is to account for BW changes in a convenient way, it should be noted that GFR is typically normalized to body surface area, since this scaling has been found to explain much of interindividual variability. Even with such normalization GFR is below adult levels near birth, rising toward adult values over the first few months (DeWoskin and Thompson, 2008). Therefore, consideration was given to scaling of renal excretion for infants by $BW^{2/3}$ as an approximation of surface area normalization and using the average values compiled by DeWoskin and Thompson (2008) for different age ranges. Values for the ratio of normalized GFR in infants vs. adults (ratio of mean infant value to adult, plotted vs. midpoint of each age range) are shown in Figure B-3, along with a simple power-function curve fit, $SGR = 0.2087 \times day^{0.23333}$, where day is the child's age in days. This function was used (a

correction factor), together with $BW^{2/3}$ scaling (default surface area-based scaling), to estimate urinary clearance for perchlorate in the infant, based on GFR as follows:

$$CLUp_{child} = SGR \times CLUp_{adult} \times \left(\frac{BW_{child}}{BW_{adult}}\right)^{2/3}$$
$$= 0.2087 \times day^{0.23333} \times 3.025 \times \left(\frac{BW_{child}}{70}\right)^{2/3} \quad \text{(Eq. B3)}$$

Clearance for iodide is similarly calculated from the adult clearance value.

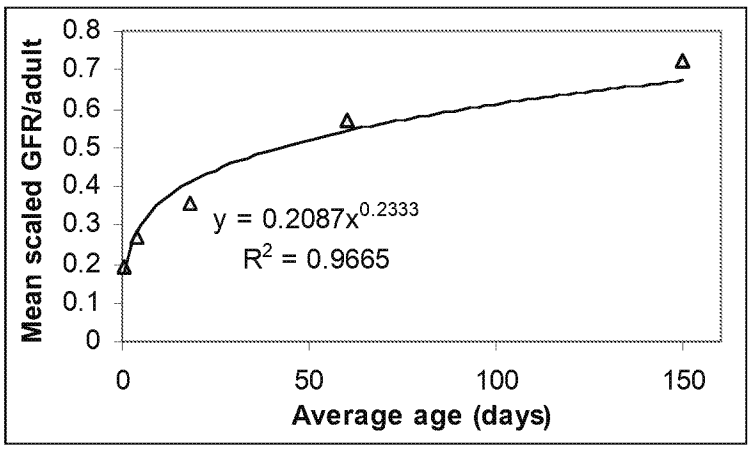

Figure B-3. Ratio of surface area-normalized GFR (mL/minute/surface-area) in infants vs. adults as a function of age.

Data from DeWoskin and Thompson (2008).

The result of applying equation B3 to the individual data of Guignard et al. (1975), but using the total adult GFR of 125 mL/minute (7.5 L/hour) instead of the iodide clearance of 3.025 L/hour, is shown in Figure B-2. The result is not a smooth function of BW because of the variation in BW vs. age in that data set. However, one can see that the resulting predictions are generally higher than the observations in that particular data set. This is not surprising since the average clearance values of Guignard et al. (1975) are lower than many of the other results included in the calculation of geometric means for each age range by DeWoskin and Thompson (2008), on which the multiplicative function shown in Figure B-3 and used in equation B3 is based. Likewise, applying equation B3 to a 7-day-old 3.6-kg infant results as follows:

$$CLU_{child} = 0.2087 \times 7^{0.23333} \times 3.025 \times \left(\frac{3.6}{70}\right)^{2/3} = 0.14 \text{ L/hour} \quad \text{(Eq. B4)}$$

Compared to the GFR of 0.21 L/hour, this seems reasonable, although it is 67% of the GFR rather than 40%. At 60 days, when an average child is 5 kg, equation B3 yields

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0.28 L/hour or 4.7 mL/minute, which also appears reasonable in comparison to the data in Figure B-1, again noting that this is iodide clearance rather than total GFR. While the data shown above are for children below 25 days, EPA extends its extrapolation to a 60-day-old 5-kg child, though with greater uncertainty at that age (since renal clearance does rise rapidly during that time). However, the estimates obtained up until 30 days are expected to be fairly sound.

B.4. Urinary Clearance in the Older Child

For older children, consideration was given to the data of Chin et al. (1982) and Lloyd et al. (1985) for cimetidine, which is primarily cleared by urinary excretion. The subjects were children being treated primarily for closed-head injuries ("secondary to motor vehicle accident"), and EPA restricted the Lloyd et al. (1985) data (larger data set) analysis to only that injury category (excluding a few cases of sepsis, for example) and to ages less than 12 years (youngest was 4.1 years). The Chin et al. (1982) data are included because they include children as young as 1 year, though there were fewer subjects. Unlike in neonates, from these data it appears that either direct BW scaling, normalization, or scaling by $BW^{0.75}$ may be appropriate. A plot of clearance/BW (y-axis) vs. BW is shown in Figure B-4, with lines indicating $BW^{1.0}$ (constant, dash-dot horizontal line with this normalization), $BW^{0.75}$, and $BW^{2/3}$ scaling from adult values.

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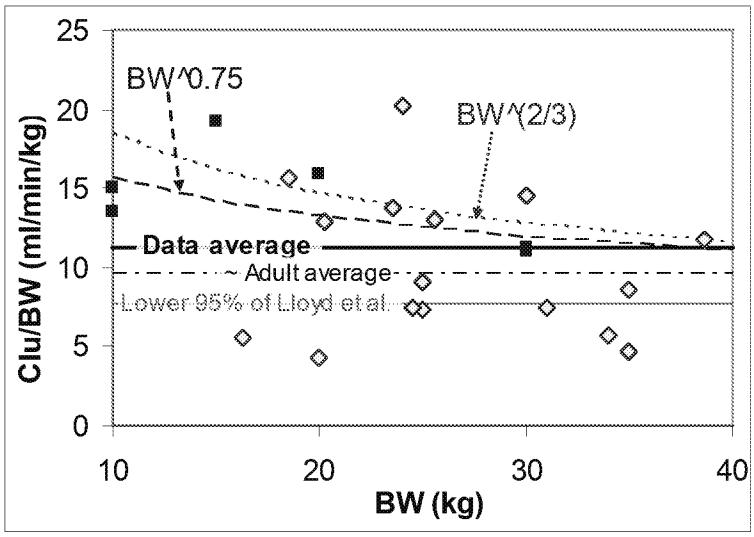

Figure B-4. Cimetidine clearance data (Chin et al. [1982] [maroon squares] and Lloyd et al. [1985] [yellow diamonds]) and possible scaling relationships.

$BW^{0.75}$ and $BW^{2/3}$ curves are normalized to BW after applying this scaling. The data average line is likewise determined by combining the normalized Chin et al. (1982) and Lloyd et al. (1985) data, irrespective of BW, calculating the average of those values, and plotting a horizontal line with that value. The lower 95% of Lloyd et al. line is likewise plotted at the lower 95% confidence limit on the mean of the Lloyd et al. data, determined from considering the normalized values as a set of samples independent of BW.

Lloyd et al. (1985) stated that the range of clearance rates in adults is 9–10.3 mL/minute-kg, and the average of these two values is shown for comparison (with no trend vs. BW) as well as the average of the data shown and the results of using $BW^{0.75}$ and $BW^{2/3}$ to scale from that approximate adult average. It can be seen that the data of Lloyd et al. (1985) (normalized to $BW^{1.0}$) show little residual trend vs. BW, although the more limited data of Chin et al. (1982) show a downward trend similar to the results of scaling by $BW^{0.75}$ and $BW^{2/3}$. (Regression of the Lloyd et al. [1985] data yields a slope that is negative but not significantly different from zero.)

While the allometrically scaled relationships are clearly within the range of the data and may be considered a reasonable estimation, the closeness of the normalized data average to that for adults and the fact that the $BW^{0.75}$ scaling falls above the data average suggest that simple scaling of Clu by $BW^{1.0}$ better describes the data over much of the range. In the face of the variability shown by these data and lack of clear fit by any of these functions, EPA chose to represent the average clearance in older (≥1 year of age) children by scaling adult clearance values by $BW^{1.0}$, although this relationship may be low for younger children. The results of using $BW^{0.75}$ scaling, as in the original publication of Clewell et al. (2007), are also shown in Table 4-2 as representing high clearance values, and the results of scaling by $BW^{1.0}$ but

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multiplying by the ratio (0.76) of the lower 95% confidence bound to the mean for the Lloyd et al. (1985) data are shown for the low clearance values.

B.5. Urinary Clearance in Pregnancy and Lactation

Clewell et al. (2007) estimated clearance of perchlorate and iodide during pregnancy and lactation based on parallel changes in the rat (vs. average adult), obtaining clearance for both compounds of about half the average adult values during pregnancy. During lactation this approach led to half of the average adult clearance for perchlorate but a value for iodide equal to that in adults. The data for iodide clearance in humans of Aboul-Khair et al. (1964) during pregnancy and early postnatal times, shown in Figure B-5, were also considered.

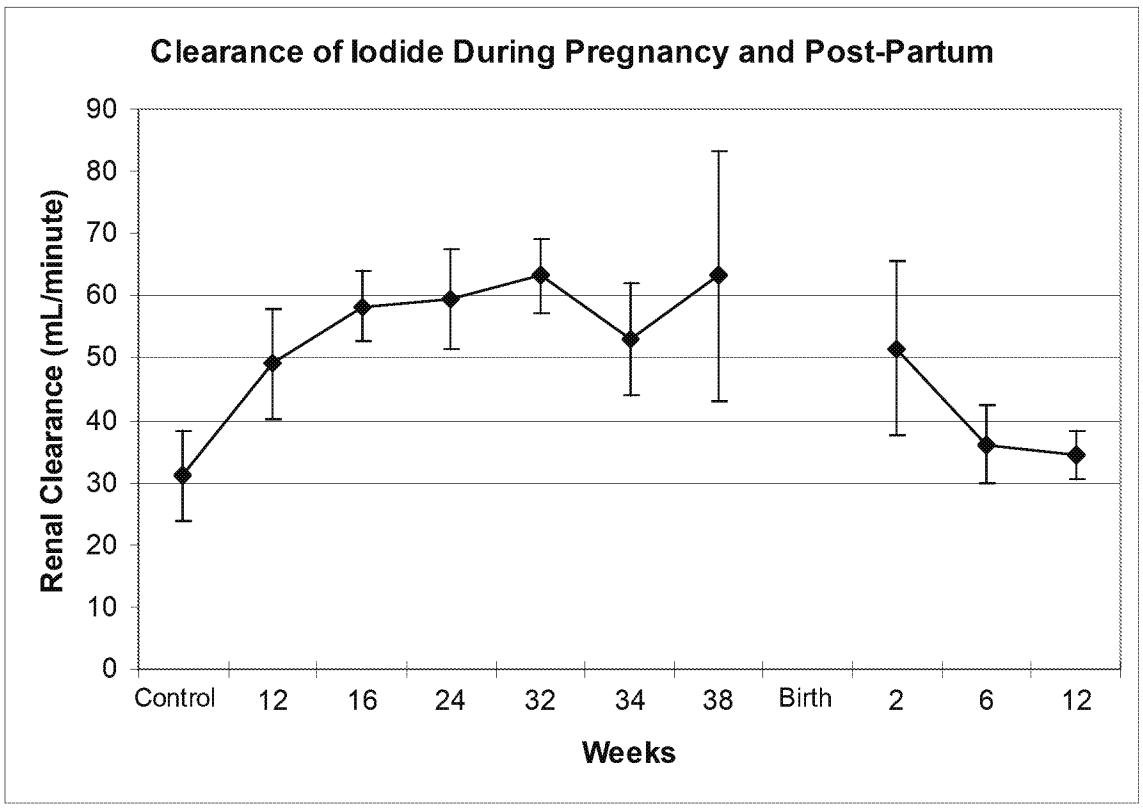

Figure B-5. Renal clearance of iodine (mean ± 2 SEM) in pregnancy and the postpartum period compared with nonpregnant, control values.

Data source: Aboul-Khair et al. (1964).

These data show that renal (urinary) clearance for iodide is elevated to as much as two times control (nonpregnant) values during pregnancy, and, while clearance then declines fairly rapidly towards control after birth, it is still elevated in the first couple of months, where EPA's analysis of neonatal clearance has focused attention. In keeping with the assumed proportionality between perchlorate and iodide and based on these data, the same relationship

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would be expected to hold as higher rather than reduced clearance. A dilemma occurs in considering the data of Aboul-Khair et al. (1964), however, in that the control iodine clearance as measured by the authors is 31.05 ± 3.66 mL/minute (mean ± standard error of the mean [SEM]), while the value determined by Merrill et al. (2005) for nonpregnant adults is 44.3 mL/minute. Likewise Aboul-Khair et al. (1964) reported thyroid iodide uptake at 2.5 hours postinjection as 21.4 ± 1.4% of the administered dose, but the amount predicted by the Merrill et al. (2005) model (in the absence of perchlorate) is 7.6%. Therefore, the data of Aboul-Khair et al. (1964) were normalized to their own controls for both urinary clearance and iodide uptake, and then that relative change was used as a model input (for clearance, multiplying the nonpregnant clearance rate constant by the pregnant:control ratio from Aboul-Khair et al. [1964]) or in estimating changes in thyroid NIS (to fit relative increases in thyroid uptake).

The urinary iodine clearance data from Aboul-Khair et al. (1964) for pregnancy and at 1 week post partum, with a quadratic interpolation function, are shown in Figure B-6. A quadratic function was likewise fit to the data for the early postnatal period (along with the last gestational data point) as shown in Figure B-7. The latter function was only used up to 60 days (8.6 weeks) of infant age, since the data indicate a decline toward control values after that point.

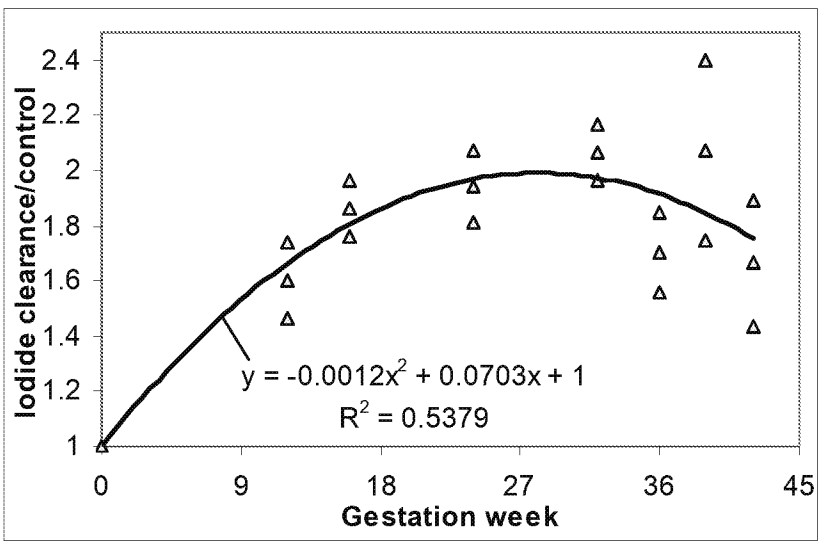

Figure B-6. Relative pregnant:nonpregnant iodide clearance values from Aboul-Khair et al. (1964), with quadratic interpolation function.

Points are mean ± SEM.

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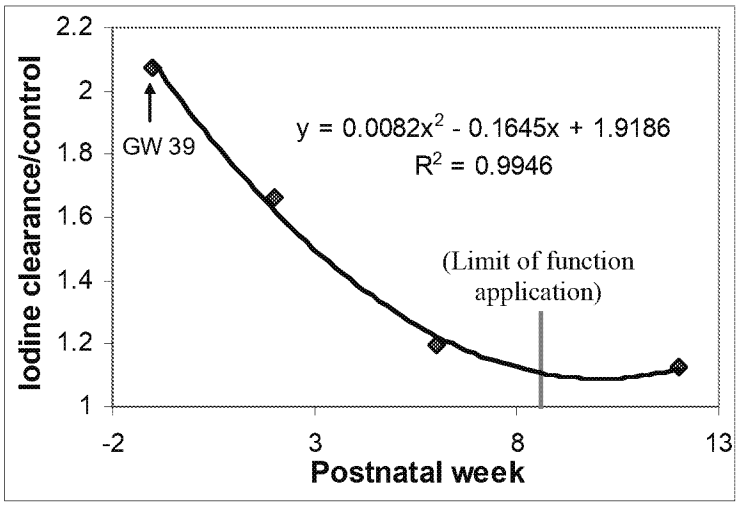

Figure B-7. Maternal iodine urinary clearance and approximation function for early postnatal period.

Data source: Aboul-Khair et al. (1964).

For pregnancy, the V_{max} values for maternal thyroid NIS-mediated uptake of perchlorate and iodide were adjusted specifically to fit iodide uptake data of Aboul-Khair et al. (1964) collected at the same pregnancy time points as the urinary clearance data. A multiplier function

$$RV_{max}(\text{pregnancy}) = 0.0009 \times GW^2 - 0.054 \times GW + 2.6 \qquad \text{(Eq. B5)}$$

was used to adjust both the perchlorate and iodide values. The fit to these iodide uptake data, given the increased urinary clearance as shown in Figure B-6 and the fitted quadratic for increased maternal NIS, is shown in Figure B-8.

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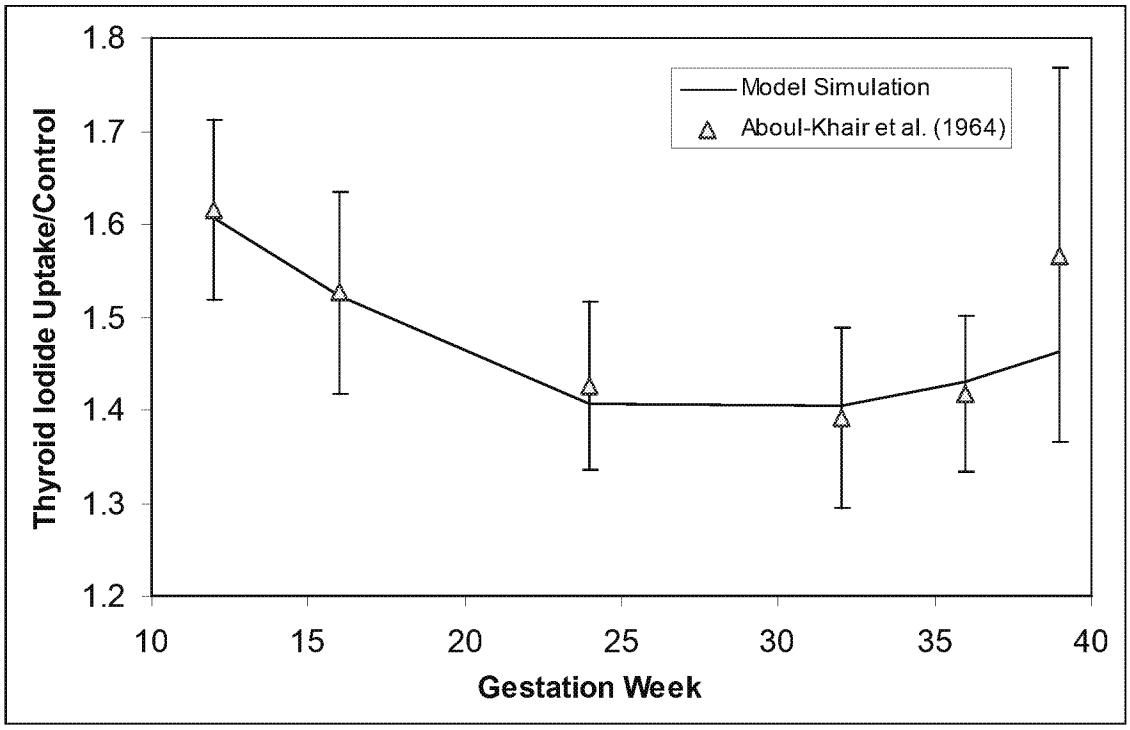

Figure B-8. Thyroid iodide uptake at 2.5 hours post i.v. injection relative to control.

Data (points) are from Aboul-Khair et al. (1964) (mean ± SEM). The line represents the model simulation. Note that, while values drop from GW 12 to 32, they are consistently greater than one.

During the postpartum period the urinary clearance and iodide uptake data of Aboul-Khair et al. (1964) are both falling toward control values, but there is the situation that the control uptake measured, 21.4% of the i.v. dose at 2.5 hours postinjection, is well above the value estimated by the PBPK model for an average adult: 7.6%. Furthermore, a number of the physiological parameters differ in the lactating woman model vs. the average adult, and are expected to change over time. Therefore, EPA first ran the lactating woman model, using the average adult clearance constants (scaled by $BW^{0.75}$) at postnatal week 50 to estimate the model-control maternal uptake at 2.5 hours post iodide injection: 6.4%. Then, to evaluate the impact of using these observations, the NIS levels during this period were adjusted by assuming that, as clearance falls from about two times control values at GW 39 (1 week prior to birth) towards control, the NIS V_{max} values follow suit, dropping to the values of Merrill et al. (2005) for the adult. In particular, if RCLF is the fold increase of urinary clearance over control, then the NIS V_{max} was multiplied by the following:

$$RV_{max}(\text{lactation}) = (RCLF - 1)^2 + 1 \qquad \text{(Eq. B6)}$$

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Thus, for RCLF = 2.09 (from the equation in Figure B-7) at GW 39 (postnatal week "–1"), RV_{max} equals 2, and, as RCLF falls towards 1.0 (i.e., clearance approaches control values), RV_{max} also falls to 1.0, so V_{max} values will approach controls. A plot of the RAIU uptake measured by Aboul-Khair et al. (1964) and the simulated values resulting from use of this function are shown in Figure B-9, where both have been normalized by their respective control values.

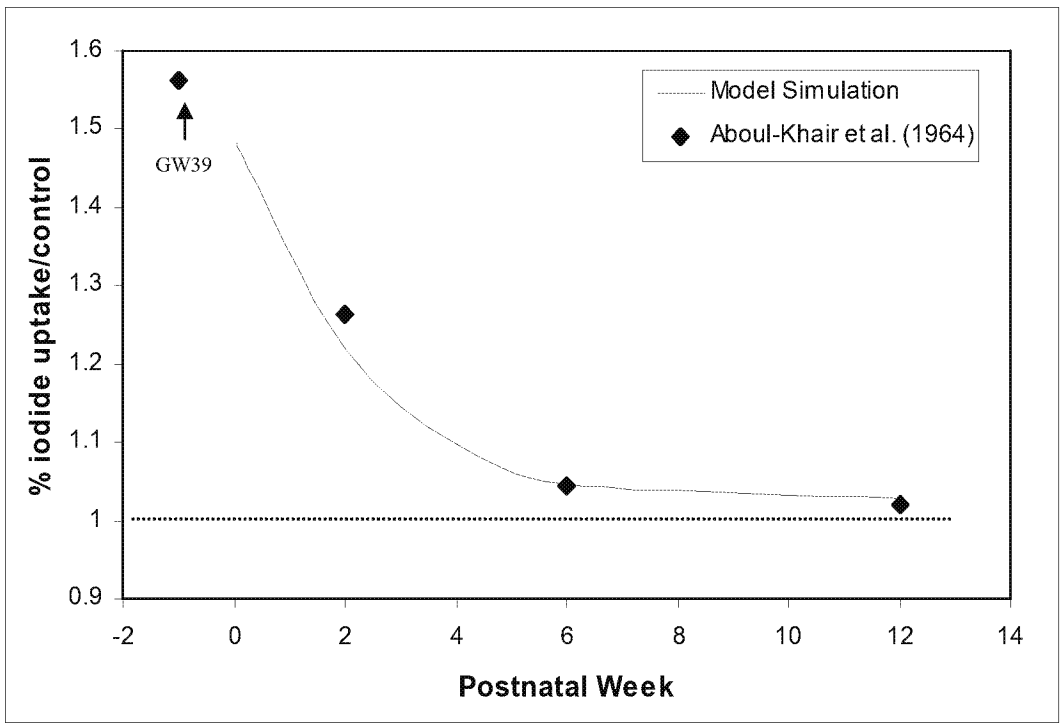

Figure B-9. Radioiodide uptake in late pregnancy and early postnatal period.

Data are from Aboul-Khair et al. (1964). PBPK simulations are with adjusted lactation model (see text above).

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APPENDIX C:
MODEL REVIEW FINAL REPORT FROM EPA CONTRACTOR

Battelle
The Business *of* Innovation

Center for Biological Monitoring & Modeling

September 25, 2008

Report for Work Assignment 4-5

Evaluation of Perchlorate PBPK Model

Submitted To:

Robert DeWoskin, PhD, DABT
US EPA/NCEA
Research Triangle Park, NC 27711

Principal Investigator:
Paul M. Hinderliter, Ph.D.
ph: 509-376-3907
fax: 509-376-9064
e-mail: paul.hinderliter@pnl.gov

Address:
Battelle, Pacific Northwest Division
902 Battelle Blvd.
P.O. Box 999, MS P7-59
Richland, WA 99352

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Overview

Battelle received PBPK models from EPA that were revised from Clewell et al. (based on the 2007 manuscript *Perchlorate and Radioiodide Kinetics Across Life Stages in the Human: Using PBPK Models to Predict Dosimetry and Thyroid Inhibition and Sensitive Subpopulations Based on Developmental Stage*) and performed the following tasks:

- Evaluated model code for internal consistency
- Digitized figures from published manuscripts
- Compared manuscript figures to current ACSL model outputs

Results

The check of the model code found no outstanding coding discrepancies beyond those corrected by EPA staff (as noted in the code/comments of the model files). Additionally, the EPA staff corrections (as identified by comments in the code) all appear to appropriately result in code equations which now reflect the model as described in the manuscript.

Model Checked:

Lactational Model **HlactFrev.csl**

Pregnancy Model **HPregF_Y_pms2.csl**

The model code has been significantly revised by EPA staff to correct mistakes (typos) in equations, harmonize model code with statements in the manuscript, clean model code for readability, and reduce model run irregularities (i.e. long simulation times). Extensive model checking by Battelle was conducted on prior versions of the csl files. The current csl files were also checked to verify that corrections/additions were properly implemented. The m-files for producing the figures are attached in the Appendix.

From the 2007 Clewell paper, the following figures were analyzed:

Figure 5 – Thyroid of newborns;

Figure 6 – Maternal Concentrations;

Figure 7 – Total fetal burden;

Figure 8 – Lactating women; and

Figure 9 – Neonatal urine.

EPA staff also provided additional parameter values and some adjusted m-files for some of the simulations as noted in the discussion of each figure.

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In addition to the output of the current model, simulation lines presented in the original manuscript were digitized (using DigitizeIt, share-it! - Digital River, Eden Prairie, MN) and are presented in most of the figures below.

In general, the model simulations were similar to, but occasionally not identical to, the published model results. This may be due to modifications made by Clewell et al. (2007) after publication or EPA's corrections to the submitted model.

Figure 5 – Thyroid of newborns:

- Produced using the **pregnancy** model and the **Fig5_GFR.m** file.
  - The figure presents model-simulated thyroid radioiodide uptake 24 h postdosing in the newborn infant.
  - The 3D nature of the manuscript figure makes it difficult to determine the exact values of the points.
  - Since the experimental data exists only at 24 hour after dosing (for each dose group), only this time point was simulated.
  - EPA staff provided additional constants not documented in the original model code (see attached Fig5_GFR.m file).
  - The simulation closely represents the published simulations and the experimental data.

Figure 5 Clewell 2007

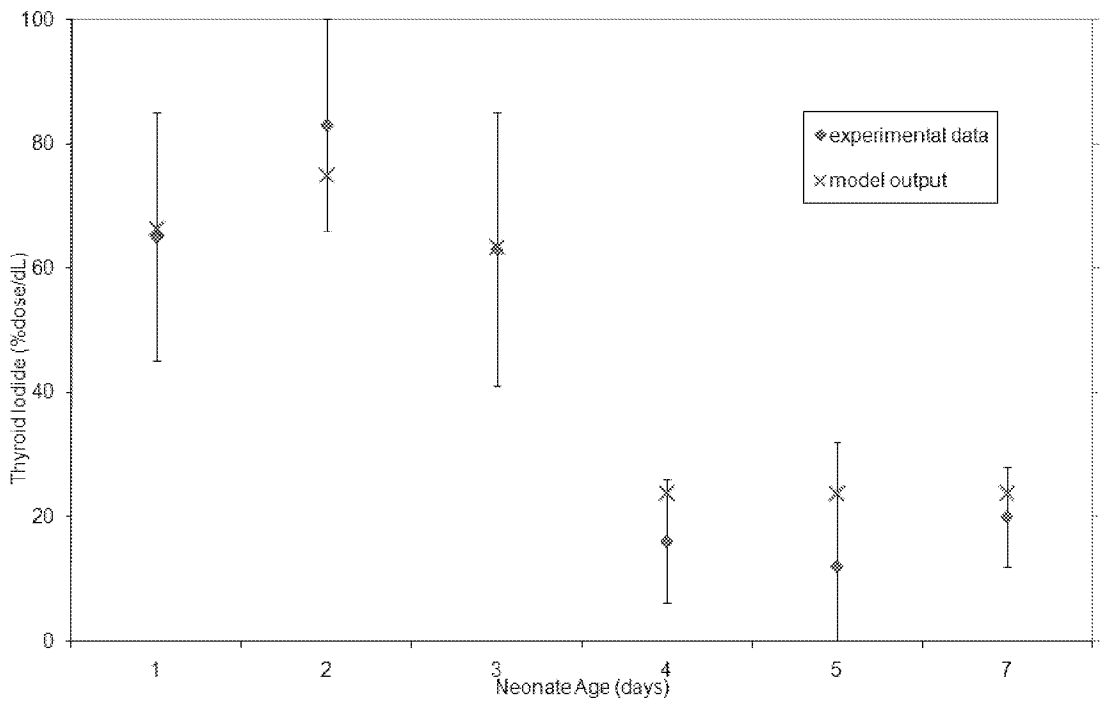

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Figure 6 – Maternal Concentrations

- Produced using the **pregnancy** model and the **Fig6.m** file.
  - The figure presents predicted radioiodide concentration in maternal (A) thyroid, (B) urine, (C) whole blood, and (D) placenta.
  - The experimental data in the m files matches that presented in the manuscript with a few minor differences for both the mean and max Vmax values.

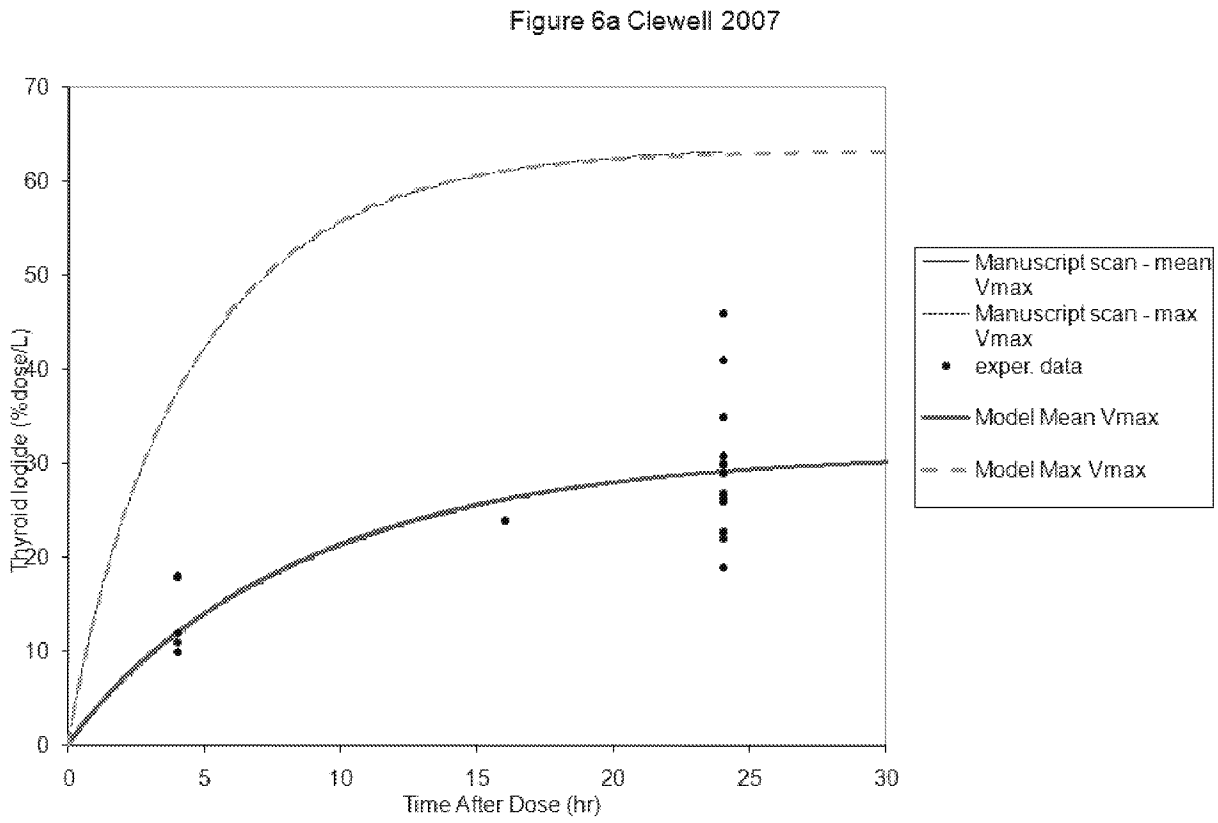

Figure 6b Clewell 2007

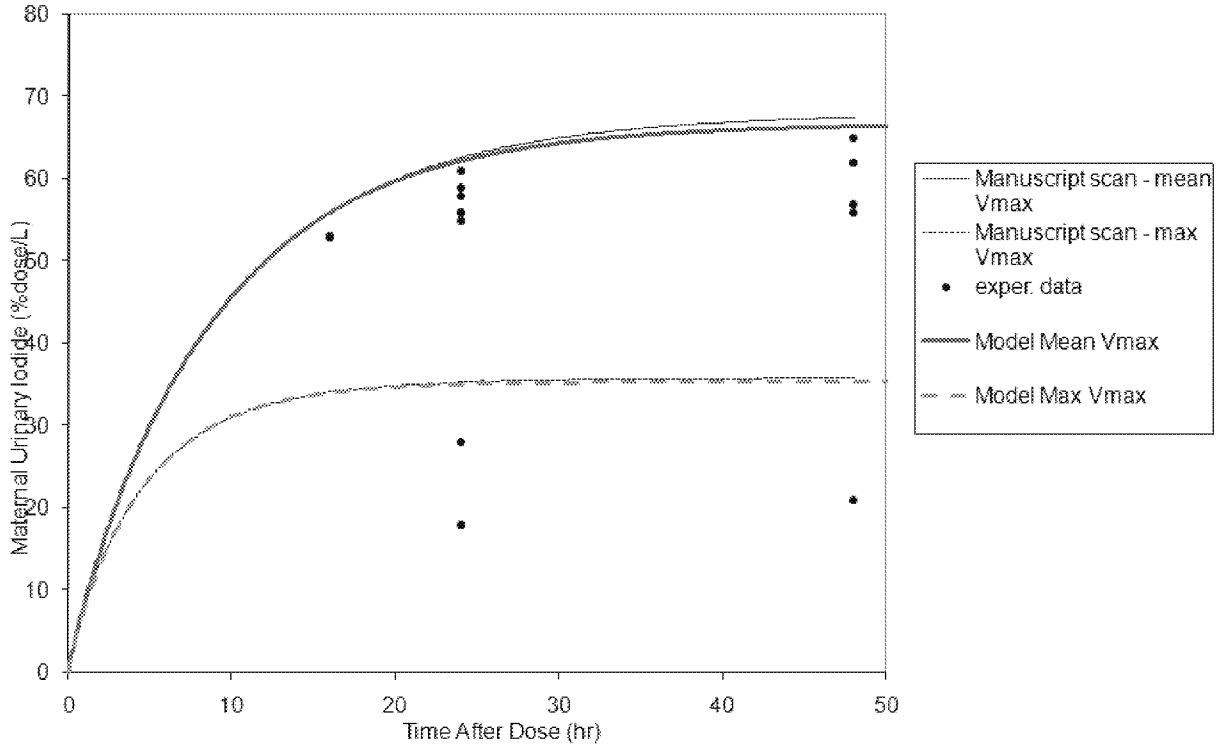

Figure 6c Clewell 2007

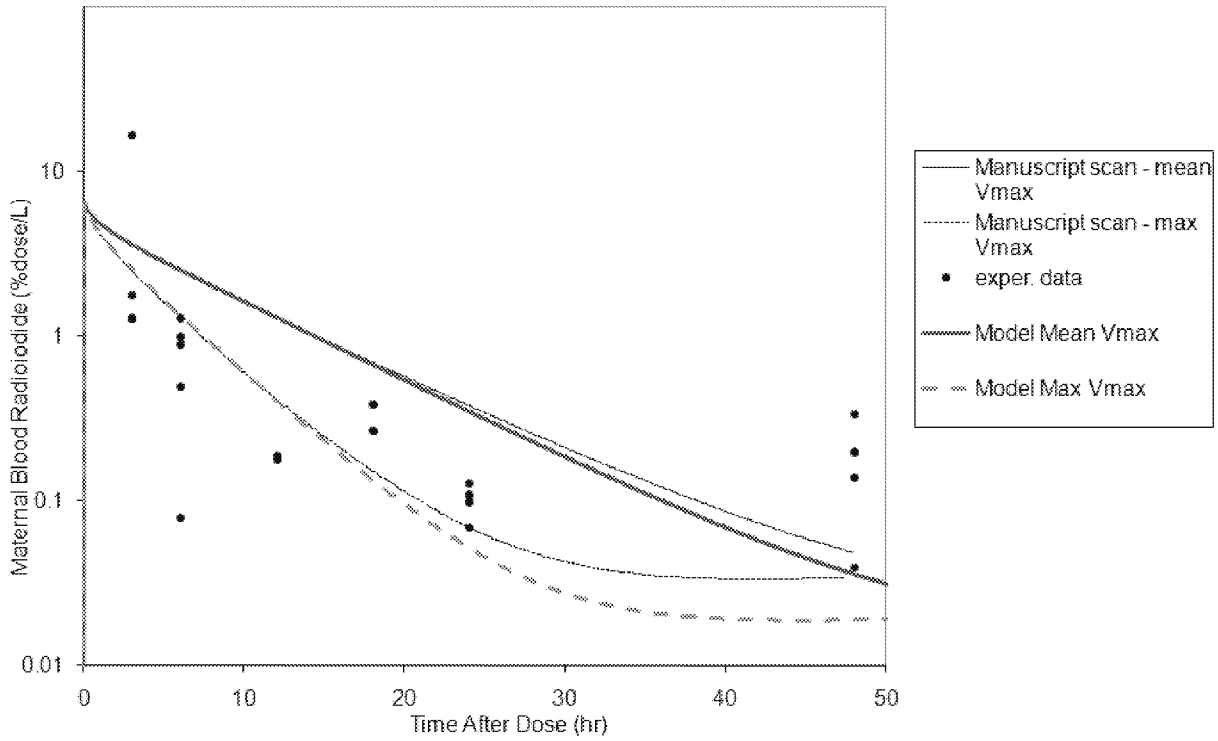

Figure 6d Clewell 2007

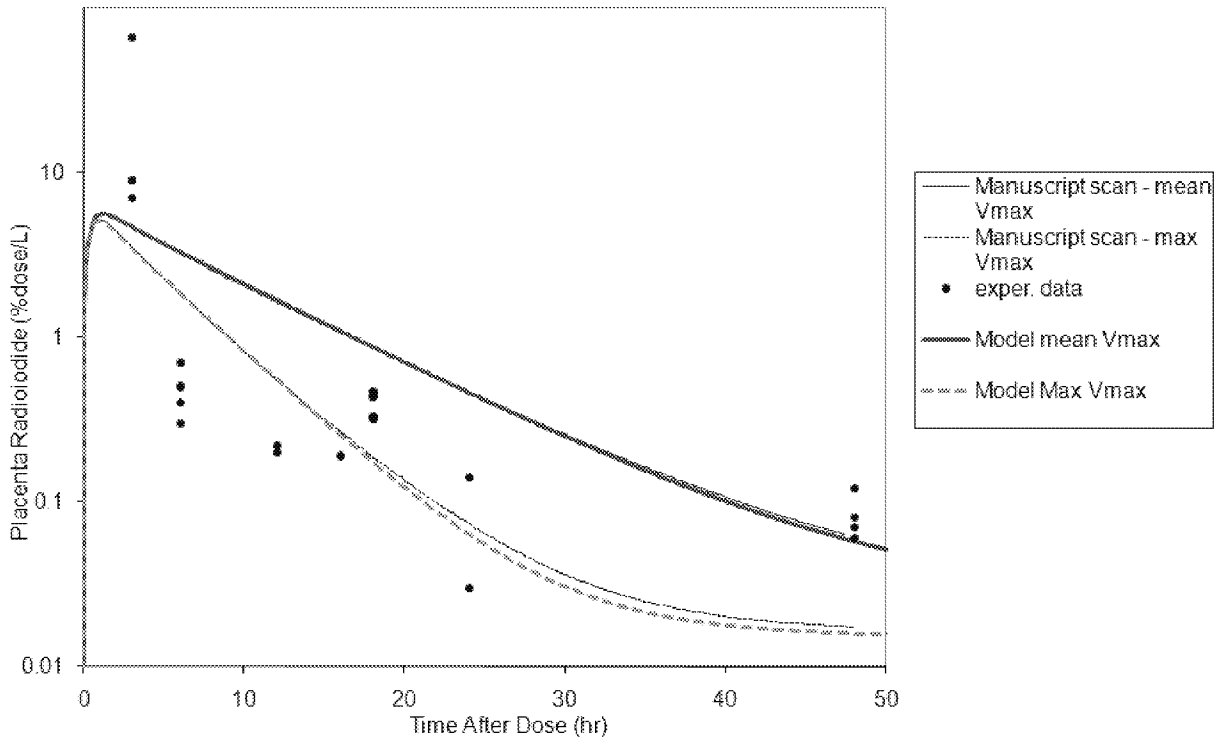

Figure 7 – Total fetal burden

- Produced using the **pregnancy** model and the **Fig7.m** file.
  - The figure presents Total fetal $^{131}I^{-}$ burden.
  - Experimental data appears to match (except for an anomalous value in the manuscript day 15 panel, at 20 hours and 90+ percent iodide in the fetus).
  - The simulation and publication differ slightly in the rate of elimination with the acslXtreme code showing slightly faster elimination.

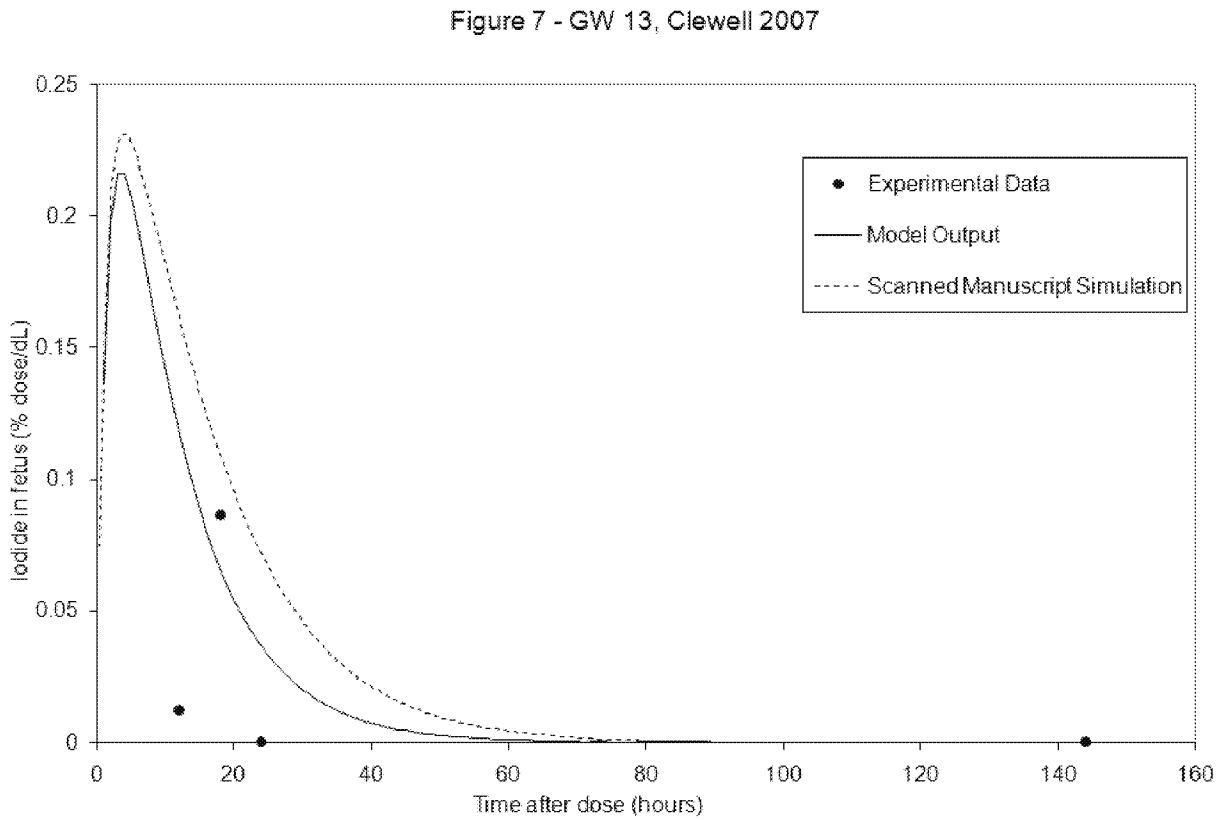

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Figure 7 - GW 14, Clewell 2007

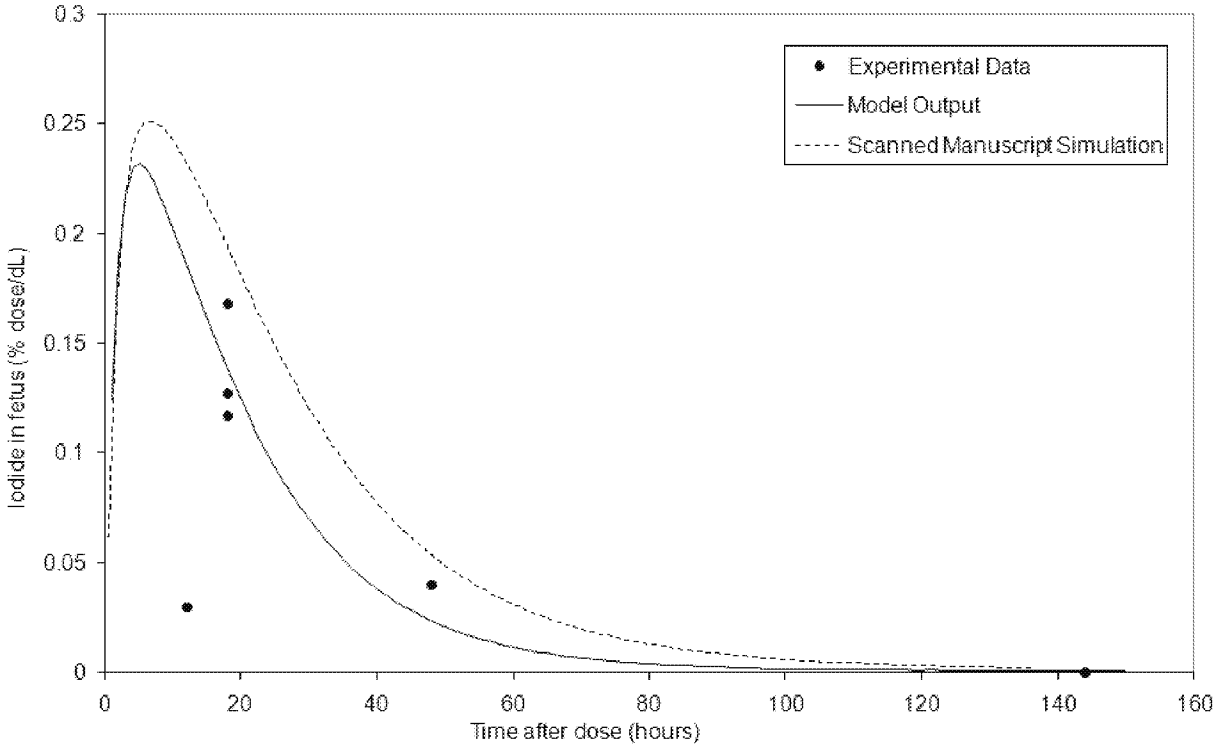


Figure 7 - GW 15, Clewell 2007

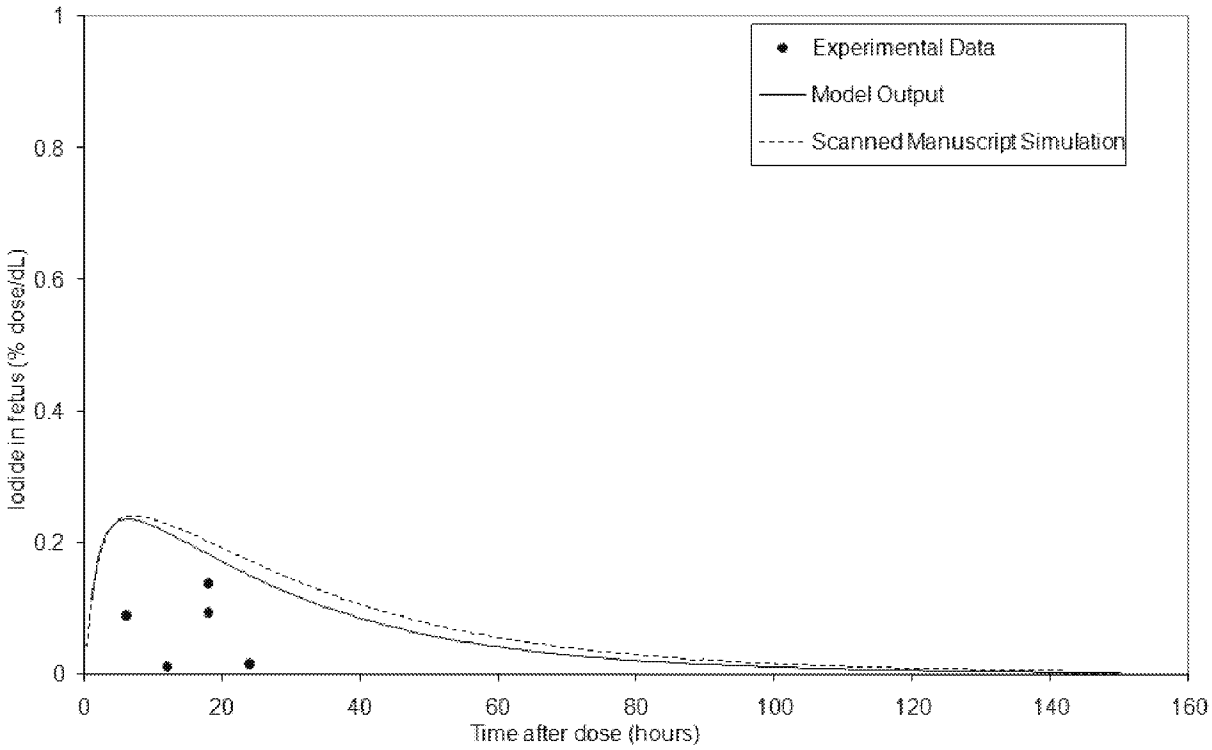


Figure 8 – Lactating women

- Produced using the **lactational** model and the **Fig7.m** file.
  - The figure presents predicted radioiodide concentration in the (A) thyroid, (B) urine, and (C) breast milk of lactating women.
  - The experimental data in the m files matches that presented in the manuscript (although there are data at longer post-dosing times in the m file not presented in the paper). EPA staff also supplied a modified m-file containing additional parameters.
  - The model simulations are close but it appears that some parameters have slightly changed.

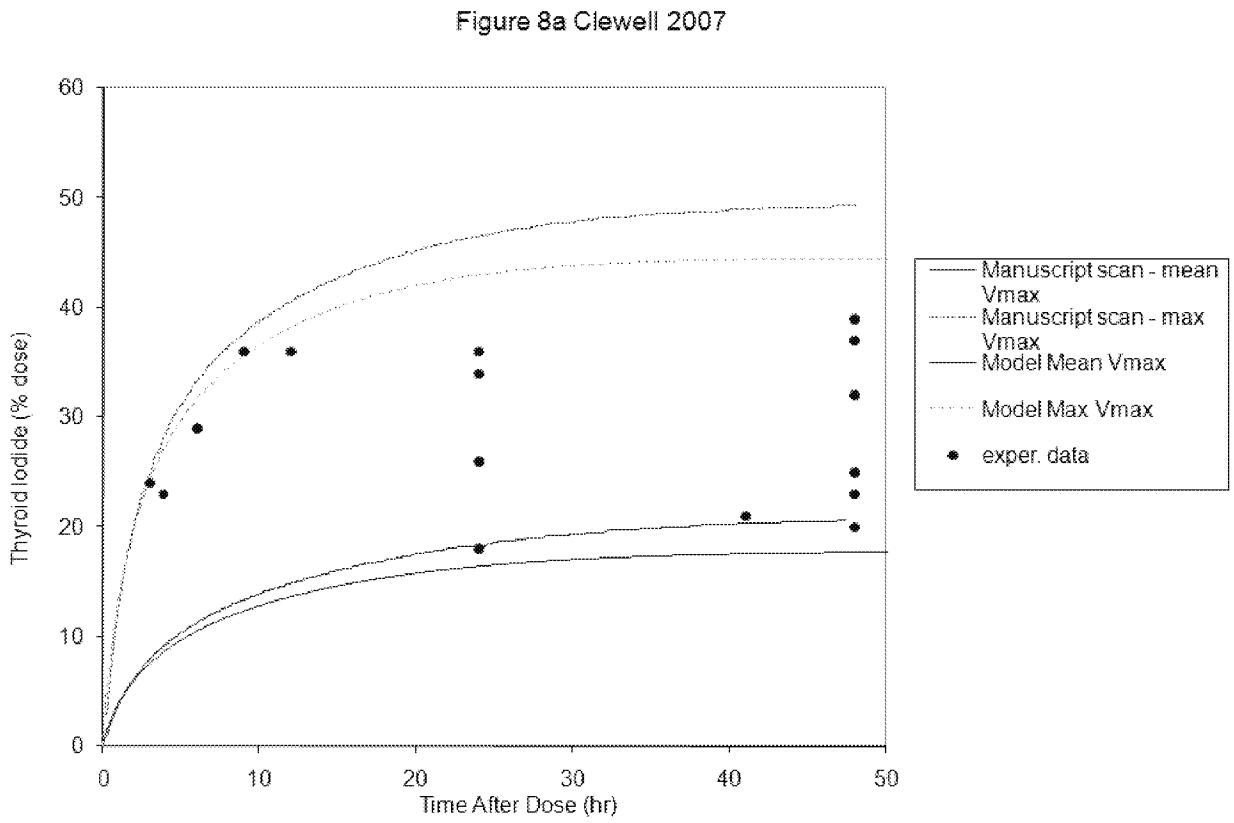


Figure 8b Clewell 2007

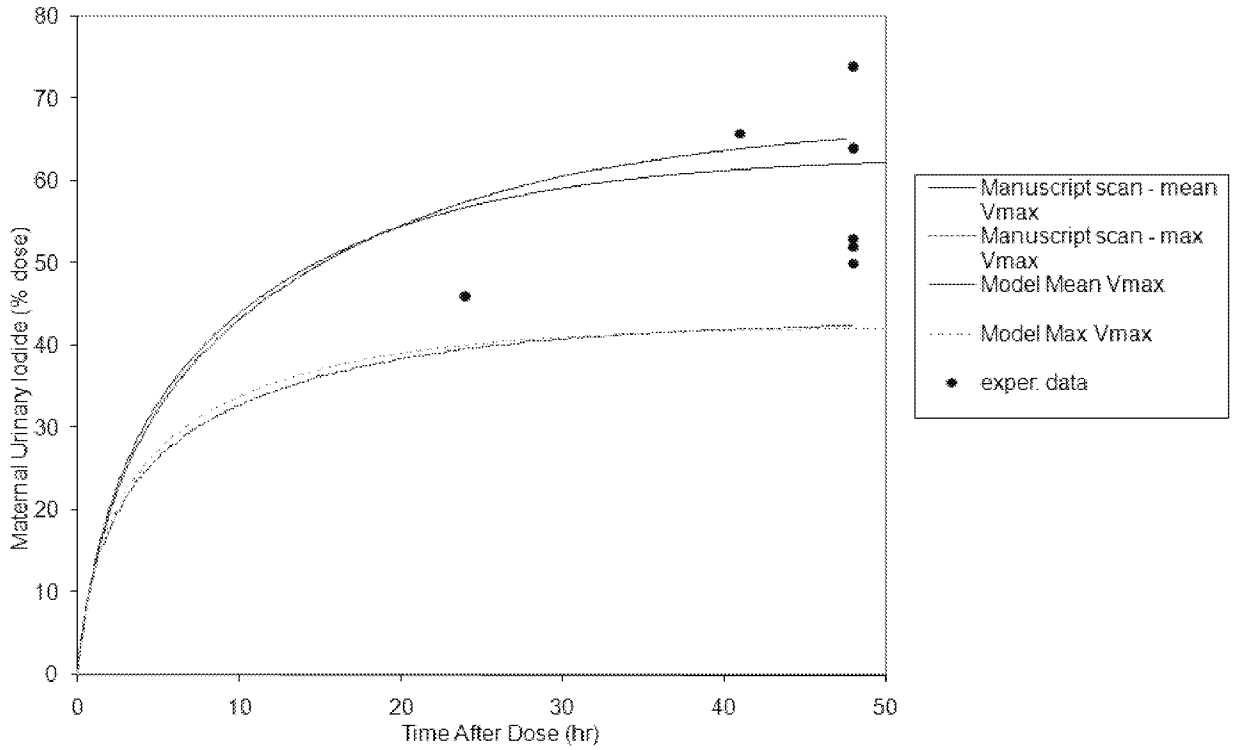


Figure 8c Clewell 2007

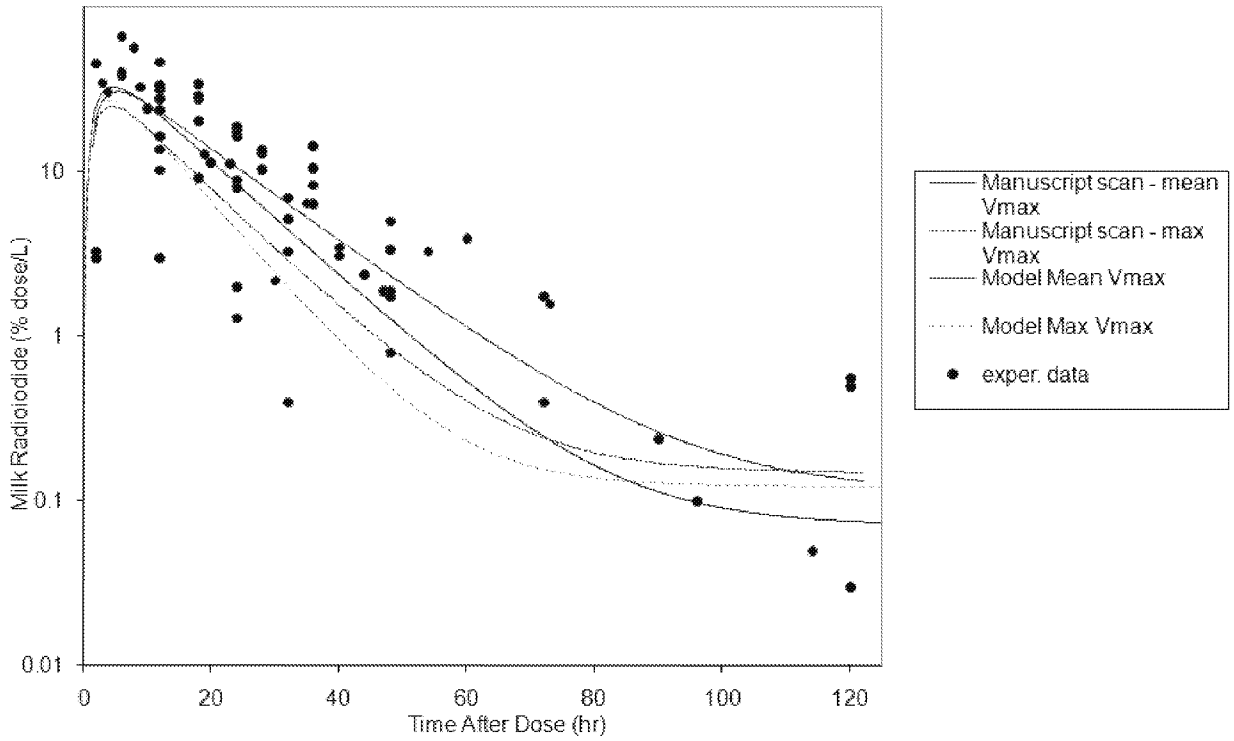
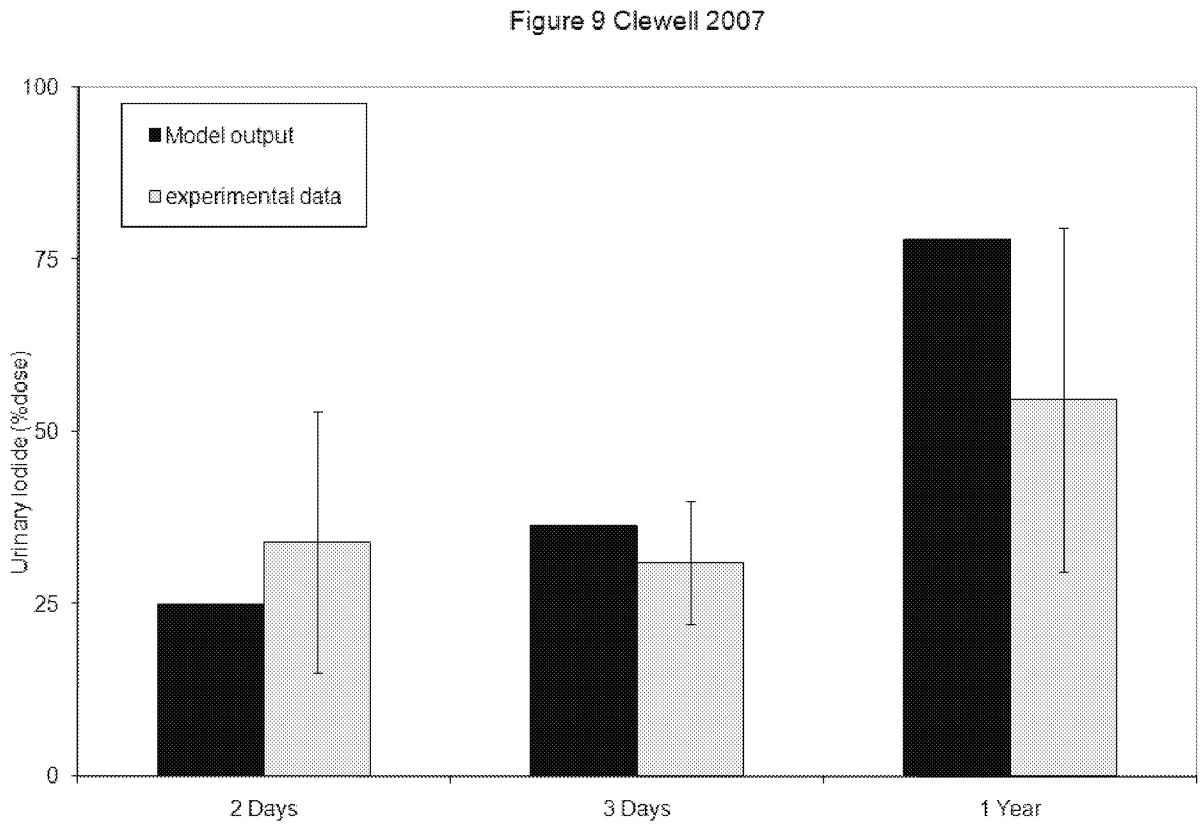


Figure 9 – Neonatal urine

- Produced using the **lactational** model and the **Fig9_GFR.m** file.
    - The figure presents predicted radioiodide in neonatal urine after a direct oral $^{131}I^{-}$ dose.
    - The experimental data in the m files matches that presented in the manuscript.
    - The model simulations closely match the simulations presented in the manuscript.



Additional Items

- Originally the pregnancy model had to run its init routine twice to get acceptable values. EPA staff fixed this issue by correcting the order of setting constant values in the m-files. The model currently does not use the init routine supplied by the original authors; rather constants are set in the csl and m-files.
- The m-files should be fully converted away from the old command language for consistency.
- Many of the figures are now easily produced by running m-files provided by the EPA staff.
- Given the evolution of the model, simulation of figures from the author's older papers on this model was attempted but the number of changes made this a difficult comparison.

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Appendix: m-files for figures

```
% Fig5_GFR.m
WESITG=0; WEDITG=0;
output @clear
prepare @clear DAYS CA_NI CTTOT_NI
nio_upt=[]; CINT=.1;
ACLU=0.75; RU=1.0; VCHNG=0.0; AKT=1; NDRNK=1;
cluc_i=0.11; cluc_p=0.125; %adult values
        CLUC_NI=cluc_i*RU*(70^(0.75 - ACLU));
        CLUC_NP=cluc_p*RU*(70^(0.75 - ACLU));
PDOSE=0; IVDOSE_I=0; IVDOSE_NI=50; PPB=0; PDOSE_N=0; CONC=0; DOSE_RI=0;
for day=[1:5,7]
        IVSTART_I=(day-1)*24; TSTOP=IVSTART_I+24; IVSTRT_NI=IVSTART_I;
        start @nocallback
        nio_upt = [nio_upt;[day, BW, BW_N, 100*ATTOT_NI/IVDOSE_NI]]
end
```

```
%maternal iodide vs. combined literature data
%corresponds to Figure 6 in JTEH, 2005
%DATA Miodide (t, au_i, attot_i, catot_i, cpl_i)
MiodideD=[3699     NaN      NaN       16.8    9
3699     NaN      NaN       1.8     66
3699     NaN      NaN       1.3     7
3700     NaN   11       NaN      NaN
3700     NaN      12       NaN      NaN
3700     NaN      18       NaN      NaN
3700     NaN      10       NaN      NaN
3700     NaN      18       NaN      NaN
3702     NaN      NaN       0.9     0.4
3702     NaN      NaN       .08     0.5
3702     NaN      NaN       1.3     0.7
3702     NaN      NaN       0.5     0.3
3702     NaN      NaN       1.0     0.5
3708     NaN      NaN       0.18    0.2
3708    NaN     NaN     0.19    0.22
3712    53      24        NaN     0.19
3714    NaN     NaN     0.27    0.32
3714    NaN     NaN     0.39    0.328
3714    NaN       NaN         NaN     0.468
3714    NaN       NaN         NaN     0.436
3720    58      46      0.1      0
3720    28      30      0.13    0.14
3720    61      22      0.11     0
3720    55      22.8    0.07    0.03
3720    59      26      0.0      NaN
3720    56      26.8     NaN       NaN
3720    18      29       NaN       NaN
3720    56      30       NaN       NaN
3720    NaN       26.4     NaN       NaN
3720    NaN       30.8     NaN       NaN
3720    NaN       29.8     NaN       NaN
3720    NaN       35       NaN       NaN
3720    NaN       41       NaN       NaN
3720    NaN       19       NaN       NaN
3744    65       NaN       0.2    0.08
3744    62       NaN       0.14   0.06
3744    56       NaN       0.04   0.12
3744    62       NaN       0.34   0.07
3744    57       NaN       0.14    0
3744    21       NaN       NaN       0
3744    62       NaN       NaN       0
3792    NaN     NaN     0.2     NaN
3792    NaN     NaN     0.22    NaN
3840    NaN     NaN     0.54    NaN
3840    NaN     NaN     0.03    NaN];

%Fig6.m
%Plot Figure 6
DOSE_I=100; TSTART=3000;IVSTART_I=696;TSTOP=800;
VMAXC_TI=1.22e5;
%VCHNG=1.7; SPLA=0;

prepare ATTOT_I AU_I CATOT_I CPL_I T
```


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```
start@nocallback
v1a=_attot_i, v2a=_au_i, v3a=_catot_i, v4a=_cpl_i, t1=_t
VMAXC_TI=6.52e5;              %maximum vmax used in merrill et al.
start@nocallback;
v1b=_attot_i, v2b=_au_i, v3b=_catot_i, v4b=_cpl_i, t2=_t


plot (t1,v1a,t2,v1b,MiodideD(:,1),MiodideD(:,3),'o','fig6a.aps')
plot (t1,v2a,t2,v2b,MiodideD(:,1),MiodideD(:,2),'o','fig6b.aps')
plot (t1,v3a,t2,v3b,MiodideD(:,1),MiodideD(:,4),'o','fig6c.aps')
plot (t1,v4a,t2,v4b,MiodideD(:,1),MiodideD(:,5),'o','fig6d.aps')
```

```
%init_preg.m -- initialization file for pregnancy
WESITG=0;WEDITG=0;
%dam clo4 (Ln 45-52), fetus ClO4 (Ln 54-60), dam I125 (Ln 62-69), fetus I125 (Ln 71-76)

!!s ps_p=0.31, pr_p=0.56, pf_p=0.05, pk_p=0.99, pl_p=0.56, pg_p=1.29, pgj_p=1.76
!!s pt_p=0.13, pdt_p=7.0, psk_p=1.32, prbc_p=0.8, ppl_p=0.56, pmam_p=0.66
!!s vmaxc_tp=6e3, vmaxc_dtp=1.67e4, vmaxc_sp=1.2e6, vmaxc_gp=3.2e7
!!s vmaxc_pp=6e4, vmaxc_mp=2.2e4, Km_Tp=1.6e5, Km_DTp=1.0e8, Km_Gp=2.0e5
!!s Km_Sp=2.0e5, km_pp=2.0e5, km_mp=2.0e5, pagc_p=0.6, pagjc_p=1.0
!!s paskc_p=1.25, patc_p=1.0e-4, padtc_p=0.01, parbcc_p=10.0, papc_p=0.1
!!s pamc_p=0.04, cluc_p=0.05
!!s vmaxc_bp=588, km_bp=1.64e4, kunbc_p=0.03

!!s ktrans2c=0.12, ktrans1c=0.12
!!s vmxc_dtfp=1.67e4
!!s padtc_fp=0.01, patc_fp=0.01
!!s Km_TFp=1.6e5, Km_GFp=2.0e5, Km_SFp=2.0e5
!!s VmxC_SFp=8.0e5, paskc_fp=1.25
!!s Vmxc_GFp=4.0e6, pagjc_fp=1.0, pagc_fp=0.66
!!s vmxc_bfp=500, km_bfp=1.8e4, kunbc_fp=0.03

!!s ps_i=0.21, pr_i=0.4, pf_i=0.05, pk_i=1.09, pl_i=0.44, pg_i=1.0, pgj_i=2.0
!!s pt_i=0.15, pdt_i=7.0, psk_i=0.7, prbc_i=1.0, ppl_i=0.4, pmam_i=0.66
!!s vmaxc_ti=1.22e5, vmaxc_dti=1.0e8, vmaxc_si=8.4e4, vmaxc_gi=4.5e5
!!s vmaxc_pi=5e4, vmaxc_mi=4.0e4, Km_Ti=4.0e6, Km_DTi=1.0e9, Km_Gi=4.0e6
!!s Km_Si=4.0e6, km_pi=4.0e6, km_mi=4.0e6, pagc_i=0.16, pagjc_i=12.0
!!s paskc_i=0.06, patc_i=1.0e-4, padtc_i=1.5e-5, parbcc_i=10.0, papc_i=0.005
!!s pamc_i=0.01, cluc_i=0.06, khormc_i=0.03, ksecrc_i=3.1e-7
!!s vmaxc_bi=300, km_bi=7.8e5, kdeiodc_i=0.021

!!s ktrans1c_i=0.12, ktrans2c_i=0.12
!!s vmxc_dtfi=6.0e7
!!s padtc_fi=1.0e-4, patc_fi=0.01
!!s Km_TFi=4.0e6, Km_GFi=4.0e6, Km_SFi=4.0e6
!!s VmxC_SFi=3.0e5, paskc_fi=0.02
!!s Vmxc_GFi=2.0e5, pagjc_fi=0.3, pagc_fi=0.1
TSTOP=1;CINT=1;
start @NoCallBack
```

```
%Fig7.m
%Figure 7 plots
Data_HPregF
init_preg
prepare @clear TIME ATTOT_I CFET_I CTTOT_FI
DOSE_I=10.0; TSTART=2100; IVSTART_I=84; TSTOP=IVSTART_I+150;
SPLA=0; start @nocallback
plot(_time-IVSTART_I,_cfet_i, ...
        ALL13d(:,1)-TSTART-IVSTART_I, ALL13d(:,3),'o','Fig7_GW13.aps')
TSTART=2300; IVSTART_I=52; TSTOP=IVSTART_I+150;
SPLA=1; start @nocallback
plot(_time-IVSTART_I,_cfet_i, ...
        ALL14d(:,1)-TSTART-IVSTART_I,ALL14d(:,3),'o','Fig7_GW14.aps')
ALL15d=[2526   190     0.09
2532   190     0.013
2532   64      0.012
2538   31.4    0.139
2538   35.2    0.0948
2538   140.3   0.0948
2538   225.2   0.139
2544   80      0.017
2544   221.    NaN
```


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```
2544    73.2    NaN
2544    173.9   NaN
2544    88.9    NaN
2544    43.1    NaN
2544    55.2    NaN];

TSTART=2400; IVSTART_I=120; TSTOP=IVSTART_I+150;
ALL15d(:,1)=ALL15d(:,1)-TSTART-IVSTART_I;
start @nocallback
t=_time-IVSTART_I;pt=t>0;
plot(t(pt),_cfet_i(pt), ALL15d(:,1),ALL15d(:,3),'o','Fig7_GW15.aps')
```

```
%Figure 8 - RClewell et al, JTEH 2006
%Maternal iodide
%t, cmk_i, attot_i, au_i
MATID=[3242     45.80   NaN     NaN
3242    3.00    NaN     NaN
3242    3.30    NaN     NaN
3243    35.00   24      NaN
3243       NaN      NaN      NaN
3243       NaN      NaN      NaN
3243       NaN      NaN      NaN
3243.84 30.81   23      NaN
3246    40.72   29      NaN
3246    39.00   NaN     NaN
3246    67.10   NaN     NaN
3246       NaN     NaN       NaN
3246       NaN     NaN       NaN
3248    57.21   NaN     NaN
3249    33.00   36      NaN
3250    24.50   NaN     NaN
3252    31.74   36      NaN
3252    28.17   NaN     NaN
3252    28.00   NaN     NaN
3252    23.92   NaN     NaN
3252    46.70   NaN     NaN
3252    10.30   NaN     NaN
3252    34.10   NaN     NaN
3252    13.80   NaN     NaN
3252    3.00    NaN     NaN
3252    16.50   NaN     NaN
3258    27.92   NaN     NaN
3258    29.30   NaN     NaN
3258    9.30    NaN     NaN
3258    34.50   NaN     NaN
3258    20.60   NaN     NaN
3259    12.90   NaN     NaN
3260    11.51   NaN     NaN
3263    11.20   NaN     NaN
3264    8.14    36      46
3264    19.22   18      NaN
3264    2.00    34      NaN
3264    1.30    26      NaN
3264    9.00    NaN     NaN
3264    16.50   NaN     NaN
3264    17.90   NaN     NaN
3264    18.70   NaN     NaN
3268    10.40   NaN     NaN
3268    13.20   NaN     NaN
3268    13.60   NaN     NaN
3270    2.19    NaN     NaN
3272    3.30    NaN     NaN
3272    5.20    NaN     NaN
3272    7.00    NaN     NaN
3272    0.40    NaN     NaN
3275    6.50    NaN     NaN
3276    10.66   NaN     NaN
3276    8.36    NaN     NaN
3276    6.40    NaN     NaN
3276    14.40   NaN     NaN
3280    3.50    NaN     NaN
3280    3.10    NaN     NaN
3281    NaN     21      65.8
```


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```
3284    2.40    NaN     NaN
3287    1.90    NaN     NaN
3288    1.74    32      50
3288    5.05    20      74
3288    0.80    25      64
3288    1.90    23      53
3288    3.40    37      52
3288    NaN     39      NaN
3288    NaN     NaN     NaN
3288    NaN     NaN     NaN
3288    NaN     NaN     NaN
3288    NaN     NaN     NaN
3294    3.29    NaN     NaN
3300    3.95    NaN     NaN
3312    1.76    29      NaN
3312    0.40    24      NaN
3313    1.58    NaN     NaN
3330    0.24    NaN     NaN
3336    0.10    26      NaN
3336    NaN     23      NaN
3354    0.05    NaN     NaN
3360    0.56    24      NaN
3360    0.50    21      NaN
3360    0.03    NaN     NaN
3378    0.01    NaN     NaN
3384    0.01    20      NaN
3408    0.43    20      NaN
3408    NaN     21      NaN
3432    0.51    NaN     NaN
3480    0.49    15      NaN
3504    0.44    NaN     NaN
3528    0.38    NaN     NaN
3552    0.33    NaN     NaN
3672    0.18    NaN     NaN
3720    0.13    NaN     NaN
3792    0.13    NaN     NaN
3960    0.07    NaN     NaN
4152    0.01    NaN     NaN     ];

%Fig8.m
%Figure 8 - RClewell et al, JTEH 2006
WESITG=0; WEDITG=0;
output @clear
prepare T CMK_I ATTOT_I AU_I
ACLU=0.75; RU=1.0; VCHNG=0.0; AKT=0.0; NDRNK=1;
cluc_i=0.11; cluc_p=0.125; %adult values
       CLUC_NI=cluc_i*RU*(70^(0.75 - ACLU));
       CLUC_NP=cluc_p*RU*(70^(0.75 - ACLU));
PDOSE=0; IVDOSE_I=100; IVDOSE_NI=0; PPB=0; PDOSE_N=0; CONC=0; DOSE_RI=0; IVDOSE_P=0;
IVSTART_I=3240; TSTOP=3365;
!! set TIME0=3240.0
VMAXC_TI = 1.39e5;
start@nocallback
cmk1=_cmk_i; attot1=_attot_i; au1=_au_i;

VMAXC_TI=7.4e5;
start@nocallback
cmk2=_cmk_i; attot2=_attot_i; au2=_au_i;
VMAXC_TI = 1.39e5;
!! set TIME0=0
plot (_t-TIME0,attot1,_t-TIME0,attot2, MATID(:,1)-TIME0,MATID(:,3),'o','Fig8a.aps')
plot (_t-TIME0,au1,_t-TIME0,au2,MATID(:,1)-TIME0,MATID(:,4),'o','Fig8b.aps')
plot (_t-TIME0,cmk1,_t-TIME0,cmk2, MATID(:,1)-TIME0,MATID(:,2),'o','Fig8c.aps')
```


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```
% Fig9_GFR.m
WESITG=0; WEDITG=0;
output @clear
prepare @clear DAYS CA_NI CTTOT_NI
nio_urine=[]; CINT=.1;
ACLU=0.75; RU=1.0; VCHNG=0.0; AKT=1; NDRNK=1;
cluc_i=0.11; cluc_p=0.125; %adult values
        CLUC_NI=cluc_i*RU*(70^(0.75 - ACLU));
        CLUC_NP=cluc_p*RU*(70^(0.75 - ACLU));
PDOSE=0; IVDOSE_I=0; IVDOSE_NI=100; PPB=0; PDOSE_N=0; CONC=0; DOSE_RI=0;
!! set TIME0=0
for day=[2 3 366]
        IVSTART_I=(day-1)*24; TSTOP=IVSTART_I+24; IVSTRT_NI=IVSTART_I;
        if day>364
                !! set TIME0=8760
                TSTOP=IVSTART_I+48     % in .cmd file, TSTOP @ 48 hr after injection for 'Proced
year1'
        end
        start @nocallback
        nio_urine = [nio_urine;[day, BW, BW_N, AU_NI]]
end
!! set TIME0=0
```


ED_005043_00078291-00086

Appointment

To: Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]
CC: Cantilli, Robert [Cantilli.Robert@epa.gov]

Attachments: Perchlorate Peer Review Report_TO 2015-22_Draft.docx; NHANES Prelim Report Summary.docx
Location: 2400 east; Ex. 6 Personal Privacy (PP)

Start: 2/14/2017 8:00:00 PM
End: 2/14/2017 9:00:00 PM
Show Time As: Busy

Recurrence: (none)

Room change to 2400 east.

Attached please find:

1. Draft peer review report. We just received and have not had the opportunity to review. Consider this a close hold until we review and discuss internally.

2. A write up of the additional three NHANES correlation runs -

   - Since TSH levels in pregnant and non-pregnant women are statistically the same, run a combined set of correlations for TSH
   - Run a correlation between fT4 and TSH in pregnant women
   - Combine data on urinary perchlorate, nitrate and thiocyanate for pregnant and non-pregnant women and evaluate for correlation in these combined data

Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

Appointment

To: Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]

CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]

Attachments: initial_cluc_p_uncertainty_results_dfk.docx

Location: DCRoomEast2339/DC-ICC-OW-OGWDW; Ex. 6 Personal Privacy (PP)

Start: 3/21/2017 7:00:00 PM

End: 3/21/2017 8:00:00 PM

Show Time As: Busy

Recurrence: (none)

Discussion topics:

Ex. 5 Deliberative Process (DP)

Attached is the revised version of the document Dustin shared last month. In the first 3 pages, this document shows our proposed strategy for estimating key model parameters that describe perchlorate, iodine, and T4 toxicokinetics and toxicodynamics. Recall that for the proof-of-concept, Dustin used synthetic data. He has now appended new pages to this document that show results obtained using actual data from the Greer et al. (2002) study that were provided by Dr. Gay Goodman.

Conference room: 2339 WJC East

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

Code: Ex. 6 Personal Privacy (PP)

Appointment

To: Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]

CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]

Location: Conference room 2400; call in Ex. 6 Personal Privacy (PP)

Start: 3/28/2017 7:00:00 PM
End: 3/28/2017 8:00:00 PM
Show Time As: Busy

Recurrence: (none)

Today?s discussion topics include an update on the following:

Ex. 5 Deliberative Process (DP)

Conference room: 2400 WJC East
Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

Message

From: Parikh, Pooja [Parikh.Pooja@epa.gov]
Sent: 3/30/2020 2:08:23 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Request for Review - Perchlorate Reg Det Withdrawal FRN
Attachments: Perchlorate Reg Det Withdrawal FR Notice 3-20-20.v2.docx - WLO comments - 3-30-20.docx

Attaching consolidated WLO comments (mine and Carrie's) on the FRN. Please let me know if you have any questions. Thanks.

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, March 20, 2020 1:59 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Request for Review - Perchlorate Reg Det Withdrawal FRN
Importance: High

Hi Pooja,

We have made some minor revisions and edits to the draft FRN for perchlorate and the new version is attached here. As you start your review of the notice please review this version and discard the old version that I sent to you on 3-19-20.

In response to you question about timing we are working towards finalizing our documents and getting concurrence from OGWDW within the next 2 weeks. The plan is to be able to submit the package to OW's front office by 4-6-20.

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Thursday, March 19, 2020 3:04 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for Review - Perchlorate Reg Det Withdrawal FRN

Thanks; I am tied up on a legal brief and other matters through Monday COB – but I should have some time to work on this starting Tuesday. Once I delve into it and get a better sense of how much work is involved, I'll be able to give you a better timeline for my review.

Just so I know – what are you all thinking in terms of timeline for withdrawal?

Will look out for the meeting invite re the HRRCA comments.

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Thursday, March 19, 2020 12:54 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: Request for Review - Perchlorate Reg Det Withdrawal FRN

Hi Pooja,

Attached you will find the draft FRN announcing the withdrawal of the Reg Det for perchlorate. Lisa has already reviewed this version, let me know what is your availability and timeline for providing your feedback to us.

Also, we will be scheduling a call with you and Carrie in the coming days to have a discussion about OGC's feedback of the HRRCA comments.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Strong, Jamie [Strong.Jamie@epa.gov]
Sent: 7/18/2019 3:20:32 PM
To: Ow Pub Tracker [OwPubTracker@cadmusgroup.com]; Brady, Catherine [brady.catherine@epa.gov]
CC: Reiley, Mary [Reiley.Mary@epa.gov]; Behl, Betsy [Behl.Betsy@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Soares, Barbara [soares.barbara@epa.gov]; Ohanian, Edward [Ohanian.Edward@epa.gov]
Subject: FW: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints
Attachments: EST_AEP_manuscript_STiCS FINAL_OGWDW&OST 7 18 19.docx; ORD_027781 OW Transmittal Form.docx

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From: Miller, Gregory
Sent: Thursday, July 18, 2019 11:19 AM
To: Strong, Jamie <Strong.Jamie@epa.gov>
Subject: RE: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Along with the Transmittal Memo, attached are the joint OGWDW/OST comments on the provided manuscript.

Greg Miller, Senior Environmental Health Scientist
Team Lead, Human Health Risk Assessment Branch
Office of Science and Technology, Health and Ecological Criteria Division
US Environmental Protection Agency, Office of Water
1200 Pennsylvania Ave, NW (MC 4304T)
Washington, DC 20460

phone: (202) 566-2310
See attached comments from OGWDW and OST.

Thanks,
Jamie

From: Ow Pub Tracker <OwPubTracker@cadmusgroup.com>
Sent: Tuesday, July 09, 2019 12:50 PM
To: Strong, Jamie <Strong.Jamie@epa.gov>
Cc: Behl, Betsy <Behl.Betsy@epa.gov>; Soares, Barbara <soares.barbara@epa.gov>; Ow Pub Tracker <OwPubTracker@cadmusgroup.com>; Reiley, Mary <Reiley.Mary@epa.gov>; Brady, Catherine <brady.catherine@epa.gov>
Subject: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Hi Jamie,

OW received the attached manuscript: **Hines – A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks** and OW Transmittal Form from ORD for Advanced Notice Review. The subject matter of the manuscript most closely aligns with the work of OST. Mary and Catherine will be coordinating the review of the manuscript across OST and with the other NWP Research POCs. Please send your comments to Mary, Catherine, and

Cadmus no later **Tuesday, July 23**. We will send a reminder two days before the review is due. Mary will forward the review to Ed Ohanian and Owen McDonough for clearance and then return the cleared review to ORD.

Please include Mary, Catherine, and Cadmus on correspondence regarding this review so that the spreadsheet tracking the manuscript reviews can be kept current. Please contact Cadmus and cc Mary and Catherine if you have questions or delays.

Thanks,

Alex Taylor | Research Analyst
The Cadmus Group LLC
3100 Clarendon Blvd, Suite 400 | Arlington, VA 22201
(703) 247-6144

From: Brady, Catherine <brady.catherine@epa.gov>
Sent: Tuesday, July 9, 2019 8:54 AM
To: Ow Pub Tracker <OwPubTracker@cadmusgroup.com>
Cc: Reiley, Mary <Reiley.Mary@epa.gov>
Subject: [EXT] FW: Deadline July 24th -- Round 2 ADVANCE NOTIFICATION - ORD-027781 Hines et al. A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Good Morning Cadmus,

Attached is a new manuscript with fact sheets and supplemental information. The correct transmittal will be sent to you later today, hopefully. In the meantime could you please send this to the POCs, OST should be the lead office for this document. Thank you!

Catherine Brady
ORISE Participant
Health & Ecological Criteria Division
U.S. EPA| Office of Water|Office of Science & Technology

From: Bahadori, Tina
Sent: Tuesday, July 9, 2019 2:00 AM
To: Reiley, Mary <Reiley.Mary@epa.gov>; Brady, Catherine <brady.catherine@epa.gov>
Cc: Ohanian, Edward <Ohanian.Edward@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Fleming, Megan <Fleming.Megan@epa.gov>; VanDrunick, Suzanne <vanDrunick.Suzanne@epa.gov>
Subject: Deadline July 24th -- Round 2 ADVANCE NOTIFICATION - ORD-027781 Hines et al. A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Dear OW Colleagues,

Attached for your policy review, please find the newest version of a manuscript authored by ORD's David Hines and his coauthors entitled, "A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks."

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

For your convenience, in addition to the revised manuscript, a file of supportive or supplemental information, an ORD fact/impact sheet, and an OW transmittal form have been attached eh **If as you review the this paper, you run across any policy show-stoppers please let me know by no later than Wednesday, July 24th.**

I look forward to hearing back from you. Please let me know if you need additional information.

With warm regards,

Tina

==========

Tina Bahadori, Sc.D.
Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

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Message

From: Burneson, Eric [Burneson.Eric@epa.gov]
Sent: 10/8/2019 3:18:58 PM
To: Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Manibusan, Mary [Manibusan.Mary@epa.gov]
Subject: FW: When you have a moment
Attachments: EO 12866 CLEAN LCRR NPRM 10-8-19.docx

Stephanie:
Per the suggestion below from Mary and Bill, can you please transmit the attached Draft FRN to EPA's OFR office with a request for an expedited review and request an expedited publication date of 10/24. We should note that the document is not yet cleared or signed but that we expect clearance and signature by Thursday.
Eric

From: Manibusan, Mary
Sent: Tuesday, October 08, 2019 10:51 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>
Subject: RE: When you have a moment

Hi Eric,

The perchlorate proposal was received by OP on May 24th and the FRN was submitted to OFR on June 10th with comments and responses delaying the publication until June 26th. With the size of the FRN being 300 pages in length, I would advise sending the document to OFR ASAP, with a request for an expedited review and publication date. As Bill indicated, it is at the discretion of OFR to grant/deny the request, but it will at least flag it as a priority. And as with the proposal, I would anticipate comments from OFR prior to publication. Please let me know if you have additional questions.

Mary

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, October 8, 2019 10:07 AM
To: Nickerson, William <Nickerson.William@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: RE: When you have a moment

Thanks Bill
On 3 we are remembering a one month lag between signature (May 23)and FRN publication (June 26) of the perchlorate proposal which we understood was due to delays in transmitting to OFR. Given the Administrator's aggressive schedule for a final rule (he had us put January in the Reg Agenda) we need to do everything we can to expedite. I realize this may not be sufficient for the OFR but I guess I am checking on what we can do to get this in their queue for publication ASAP. Note that the FRN is over 300 pages in length.
Eric

From: Nickerson, William
Sent: Tuesday, October 08, 2019 9:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: RE: When you have a moment

I assume 1 and 2 are inevitable.

On 3, we can quickly transmit to OFR and expeditiously deal with any edits that come back. Are you looking for something more than that? It is possible to send a package to OFR with a request to expedite, but OFR is pretty strict about offering a good reason for that (because it's important isn't enough).

Copying Mary in case she has been in contact with OW WPS already on this.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, October 07, 2019 6:33 PM
To: Nickerson, William <Nickerson.William@epa.gov>
Subject: When you have a moment

Bill
I need to check in with you about

1. expedited loading of the final FRN /EA in to ROCIS for the LCRR and
2. expedited processing of the FRN for Autopen signature in time for Thursday's rollout by the Administrator
3. expedited FRN processing following Administrator's signature to assure we don't have a significant lag before publication.

Perhaps the OW WPS staff have already worked this through but I wanted to be certain its on OP's radar.
Can we talk in the morning?
Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Strong, Jamie [Strong.Jamie@epa.gov]
Sent: 3/7/2019 5:18:53 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Miller, Gregory [Miller.Gregory@epa.gov]
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED
Attachments: EST_AEP_manuscript_DID_v5a gMiller edits.docx; ORD_027781 Hines OW Transmittal Form v5a _ OST.DOCX

And looks like Rajiv...here is the last version I saw.

From: Strong, Jamie
Sent: Monday, December 10, 2018 10:04 AM
To: Behl, Betsy <Behl.Betsy@epa.gov>
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

Already sent this to you and Ed...is there something new?

From: Strong, Jamie
Sent: Tuesday, November 27, 2018 1:52 PM
To: Behl, Betsy <Behl.Betsy@epa.gov>; Ohanian, Edward <Ohanian.Edward@epa.gov>
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

Both OGWDW and Greg indicate concerns have been addressed.

From: Miller, Gregory
Sent: Tuesday, November 27, 2018 1:49 PM
To: Strong, Jamie <Strong.Jamie@epa.gov>
Subject: RE: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

Minor comments and transmittal memo attached.

From: Strong, Jamie
Sent: Tuesday, November 27, 2018 12:26 PM
To: Miller, Gregory <Miller.Gregory@epa.gov>
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

FYI

From: Christ, Lisa
Sent: Tuesday, November 27, 2018 12:26 PM
To: Strong, Jamie <Strong.Jamie@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>

Subject: RE: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

Hi Jamie,
Rajiv completed a review and found the revisions addressed the concerns raised by OW. We have no additional comments.
Thank you,
Lisa

From: Strong, Jamie
Sent: Monday, November 26, 2018 9:23 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

FYI this paper using perchlorate as a case study is back, revised per our conversation. Greg is reviewing for us, who should he coordinate with in OGWDW?

Thanks,
Jamie

From: Behl, Betsy
Sent: Monday, November 26, 2018 8:47 AM
To: Strong, Jamie <Strong.Jamie@epa.gov>
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

FYI

From: Bahadori, Tina
Sent: Sunday, November 25, 2018 1:28 PM
To: Ohanian, Edward <Ohanian.Edward@epa.gov>; Reiley, Mary <Reiley.Mary@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Cc: vanDrunick, Suzanne <vanDrunick.Suzanne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>
Subject: FW: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

Dear OW Colleagues,

I hope you had a wonderful Thanksgiving weekend! As you see in the email below from Ron Hines, David Hines and colleagues revised the manuscript "*A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks*" that was previously sent to OW as part of Advanced Notification Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

The revised manuscript, manuscript information sheet, and supporting information files are attached. Please look at this package and let us know how you would like to move this through OW's review process as expeditiously as possible. Needless to say, we would like to get this manuscript to the journal as soon as possible.

Many thanks – and looking forward to hearing back from you.

Tina

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Tina Bahadori, Sc.D.
Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

From: Hines, Ronald
Sent: Saturday, November 24, 2018 9:01 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Rodan, Bruce <rodan.bruce@epa.gov>; Fleming, Megan <Fleming.Megan@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Fisher, Bill <Fisher.William@epa.gov>; Saterson, Kathryn <Saterson.Kathryn@epa.gov>; Rashleigh, Brenda <Rashleigh.Brenda@epa.gov>; Franzosa, Jill <Franzosa.Jill@epa.gov>; Frithsen, Jeff <Frithsen.Jeff@epa.gov>
Subject: ADVANCE NOTIFICATION - ORD-027781 Hines et al. Combined AEP/AOP Framework for Cumulative Risk Assessment - REVISED

Good morning Tina,

Please find attached a revised copy of ORD-027781 Hines et al. entitled "A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks." As I am sure you recal Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

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In a briefing with the Office of Water held October 19, 2018, each of these points were addressed with the following outcomes:

Ex. 5 Deliberative Process (DP)

4.

5. Ex. 5 Deliberative Process (DP)

All of the above have been addressed in the revised manuscript consistent with the above discussions at the October 19, 2018 briefing.

Ex. 5 Deliberative Process (DP)

Please find enclosed a revised manuscript, a document with supporting data, and an Office of Water transmittal form. Please let me know if you have any questions.

Ron Hines, PhD
Associate Director for Health
US EPA, NHEERL
109 T.W. Alexander Dr., MD 305-02
Research Triangle Park, NC 27711
Tel: 919 541-5622
Cell: 919 257-8896

1. **Manuscript Title:** A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks
2. **Background/Overview:** Exposure to environmental contaminants can lead to adverse outcomes in humans as well as important non-human species. However, evaluating risk across multiple species in a contaminated environment can be challenging due not only to differences in toxicity mechanisms in response to a given target site exposure (TSE), but also to features of relevant exposure pathways that result in a different TSE. These features can include habitat, behavior, physiology, and anatomy, and can vary widely across relevant non-human organisms. This study develops mechanistic techniques to quantitatively address some of the challenges of integrating human health and ecological endpoints into risk assessments by combining the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks.
3. **Relevancy to National Research Program needs/priorities:** This paper contributes to the Human Health Risk Assessment project "Approaches to cross-species data integration to support cumulative risk assessment (CRA)" (HHRA task 6.1, RMS ID# HHRA 3.231), and develops techniques that are relevant to risk assessment and decision making. For example, the Office of Chemical Safety and Pollution Prevention (OCSPP) in support of the revised TSCA is now more routinely considering different exposure use cases and targeting ecological assessments as well as human risk assessment; and the Office of Air Quality Planning and Standards has to evaluate risk across multi-media pathways in the Risk and Technology Review (RTR) program.
4. **Name(s) of OW reviewer(s) of earlier drafts/OW co-authors, if any:** Samuel Hernandez-Quinones, Gregory Miller, and Lisa Christ
5. **Major observations and results:** The case study presented in this work accomplishes the following: 1) predicts environmental concentrations and external exposure in multiple species at a hypothetical site; 2) quantifies species-specific relative source contribution under different illustrative exposure scenarios; 3) demonstrates the linkage between external exposures, internal doses (target site exposures), and mechanistic toxicity endpoints; 4) highlights how the joint AEP-AOP construct can identify data gaps along a source-to-outcome continuum; and 5) provides an example of how the AEP-AOP approach can help to quantify uncertainties in risk predictions.
6. **Potential implications of the findings** Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

7. **Findings advancing existing scientific knowledge:** The AEP-AOP construct and analysis presented in this work advance scientific knowledge by 1) demonstrating the utility of this approach for integrating human health and ecological endpoints into CRA, 2) providing an example of how this tool can identify knowledge gaps and quantify uncertainties, and 3) proposing techniques for future placed-based risk assessments.
8. **Publication information (journal, book) and estimated timelines:** Once cleared, this manuscript will be submitted to *Environmental Science & Technology* for publication consideration. Although the time for peer review and manuscript processing varies considerably from one journal to another, the manuscript likely will appear on-line within 2 to 4 months and in print within 6 to 8 months.

9. **Has OW's review/clearance process identified any policy statements or factual errors within the draft manuscript? If yes, please specify:**

Ex. 5 Deliberative Process (DP)

10. **Date of ORD's review/clearance request received:**
    11/25/18

11. **Date of OW's completion of review/clearance:**
    11/28/18

12. **Attach incoming manuscript and fact sheet (including technical comments/factual errors, if any)**
    Please see accompanying redline for minor edits.

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/22/2019 6:46:05 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: FW: ORD workgroup draft deliberative comments on the Proposed Perchlorate Rule
Attachments: Perchlorate Rule FRN 2-4-19_ORD_v2.docx

FYI.

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

"USEPA Protecting Human Health and the Environment"

From: Flowers, Lynn
Sent: Friday, February 22, 2019 1:31 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Shao, Nicole <Shao.Nicole@epa.gov>; Burden, Susan <Burden.Susan@epa.gov>; Hauchman, Fred <hauchman.fred@epa.gov>
Subject: ORD workgroup draft deliberative comments on the Proposed Perchlorate Rule

Sam (and Eric):
Thank you for the opportunity to provide scientific comments on the FRN for the Proposed Perchlorate Rule.
I am attaching comments from our internal review group for your consideration.
Thank you for the extra time. Please let us know if you have any questions.

Reviewers included the following: Paul Schlosser, Dustin Kapraun, Hisham El-Masri, Mary Gilbert, Santhini Ramasamy, Linda Phillips and Lynn Flowers.

Please note that an additional one-pager will follow (ASAP – expect Monday) for your consideration regarding the potential uncertainty associated with intrahuman variability in the perchlorate assessment. Some of the comments in the attached FRN address this potential uncertainty.
Thanks!
Lynn

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Policy, Office of Research and Development
US Environmental Protection Agency
Washington, DC
202-564-6293

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 2/21/2019 2:38:12 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: FW: Request for review - Draft Perchlorate Rule Proposal
Attachments: Version-Control Perchlorate Rule FRN 2-4-19_aj.docx

FYI

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

"USEPA Protecting Human Health and the Environment"

From: Johnson, Ann
Sent: Friday, February 15, 2019 11:53 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Dockins, Chris <Dockins.Chris@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: RE: Request for review - Draft Perchlorate Rule Proposal

Sam,

Thank you for the opportunity to review the notice.

Attached are my comments. Please note that they're staff-level and don't reflect any input from senior management. The vast majority of the comments are editorial for your consideration, although I've flagged a few comments (with [redacted]) that are a bit more substantive. You'll see that I spent more time on some parts of the notice than I did on others. Chris Dockins is reviewing the EA-related material, and I have comment on any of that.

I'm out today, but am happy to explain any of my comments or provide any assistance next week.

Have a great holiday weekend!

Ann

From: Hernandez-Quinones, Samuel
Sent: Monday, February 4, 2019 10:32 AM
To: Johnson, Ann <Johnson.Ann@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>; Shao, Nicole <Shao.Nicole@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Foster, Stiven <Foster.Stiven@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Request for review - Draft Perchlorate Rule Proposal

Preliminary draft for internal EPA review

Hi,

Attached for your review is the Draft Perchlorate Rule Proposal (Preamble and Regulatory Text). As discussed previously we are asking that you provide your questions and or comments on the draft document to me by COB 2/15/2019. In order to keep with the consent decree deadline, we need to complete this step of the process within two weeks, if there are any issues that require technical discussions please let me know so that we can arrange any necessary working meeting.

I will follow-up with another email later today that contains the draft version of the technical support documents that were used as the basis for the Perchlorate proposal. Since those are very lengthy documents we are not requesting that you submit input and/or comments on those within the two- week time frame.

Please let me know if you have any questions.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Shao, Nicole [Shao.Nicole@epa.gov]
Sent: 7/3/2018 3:46:30 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Revised Chapter 3 Approaches Report
Attachments: WA459_T4_Vol1 Main ReportCOMMENTS_180430.ps.docx

Hi Sam,

Attached are some suggestions from Paul on the revised Ch 3. He is fine with the revisions to Appendix A. Lynn wants to look at the revised Ch 3, but hasn't had a chance yet. What's the latest she can get you something?

Re: the revised Appendix A, there was one comment from Emma's 5/3/18 e-mail I didn't see incorporated (1st paragraph).

Ex. 5 Deliberative Process (DP)

Thanks,
Nicole

Nicole Shao
US EPA, ORD-Office of Science Policy
1200 Pennsylvania Avenue, NW (8104R)
Washington, DC 20460
(202) 564-6779

From: Hernandez-Quinones, Samuel
Sent: Friday, June 15, 2018 1:48 PM
To: Shao, Nicole <Shao.Nicole@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Cc: Flowers, Lynn <Flowers.Lynn@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: Revised Chapter 3 Approaches Report

Hi Attached you will find the revised version of the approaches report. I received your comments that were incorporated in the appropriate appendix. I wanted to verify if NCEA had any comments/edits/revisions that you wanted incorporated only into Chapter 3 of the report. My understanding from previous interactions was that there were no edits needed, but please let me know if this is the case.

I am not in a hurry to finalize this report, but I would appreciate it if you can send any input to us in the next 3 to 4 weeks.

Thank You
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water

Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

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Message

From: Flowers, Lynn [Flowers.Lynn@epa.gov]
Sent: 10/24/2017 5:54:59 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
CC: Bussard, David [Bussard.David@epa.gov]
Subject: RE: DRAFT FINAL MCLG Approach Charge 20171024.docx

Thanks Lisa. After a quick read, these changes seem OK. I'll get back with you before Thursday after checking with others.

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Policy
US EPA
Washington, DC
202-564-6293

From: Christ, Lisa
Sent: Tuesday, October 24, 2017 12:54 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Bussard, David <Bussard.David@epa.gov>
Cc: Behl, Betsy <Behl.Betsy@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: DRAFT FINAL MCLG Approach Charge 20171024.docx

All,
The team has reviewed the comments received on the charge from: SBA, NASA, AWWA, DOD, NASA, AMWA and Intertox/PSG and made the attached revisions. Many of the comments were repeats of previous concerns – some already addressed. We meet with OSA this Thursday for final peer review panel selection and we can task the panel once the charge is final. Please send any comments/edits NLT Thursday COB. Let me know if you want to see the incoming comments…
Thank you in advance
Lisa

From: Hafez, Ahmed
Sent: Tuesday, October 24, 2017 10:57 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>
Subject: DRAFT FINAL MCLG Approach Charge 20171024.docx

Hi Lisa,

Please find the attached revised version of the Perchlorate charge. Based on the comments received, the revisions were minor and mostly clarifying in nature.

Let me know if you have any questions or would like to discuss of the edits.

Regards,
Ahmed

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

"It is better to do things that you cannot explain, than to explain things that you cannot do."
--Nassim Taleb

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 9/12/2017 7:59:11 PM
To: Cantilli, Robert [Cantilli.Robert@epa.gov]; Chiu, Enid [Chiu.Enid@epa.gov]; Crofton, Kevin [Crofton.Kevin@epa.gov]; Dockins, Chris [Dockins.Chris@epa.gov]; Euling, Susan [Euling.Susan@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Foos, Brenda [Foos.Brenda@epa.gov]; Foster, Stiven [Foster.Stiven@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]; Harmon, Kenneth [Harmon.Kenneth@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Jones, Joel E. [Jones.Joel@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Kirk, Andrea [Kirk.Andrea@epa.gov]; Li, Corine [Li.Corine@epa.gov]; Macler, Bruce [Macler.Bruce@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Morrison, Kendra [Morrison.Kendra@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Schutz, Michelle [Schutz.Michelle@epa.gov]; Cooperstein, Sharon [Cooperstein.Sharon@epa.gov]; Skaar, Christina [Skaar.Christina@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; El Burai Felix, Alia [ElBuraiFelix.Alia@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]; Townsend, Clifton [Townsend.Clifton@epa.gov]
Subject: Perchlorate Workgroup
Attachments: WA459_T3_Vol1 Main Report_170908.pdf; WA459_T3_Vol2 AppendixA BBDRModel_170908.pdf; WA459_T3_Vol3 AppendixB-G_170908.pdf; DRAFT FINAL MCLG Approach Charge 9-5-17.pdf

Perchlorate Workgroup,

Hi I am Sam Hernandez, I will be leading the Office of Water Team working on the Perchlorate Rulemaking Activities. I look forward meeting and working with each one of you. I wanted to provide a few updates on the activities leading to the Peer Review effort for the latest support materials for the project.

The Peer Review package was signed off by OW leadership last week, and I expect the Notices and Supporting Materials to be published in the Federal Register in the coming days. I am attaching courtesy copies of the materials to be published in the FRN, but please keep a close hold of these since these have not been officially released. I will send the working group a note as soon as the materials are publicly posted in the Federal Register.

Also, tomorrow's workgroup meeting is cancelled. I will set up a Workgroup Meeting once the notices are posted to discuss the peer review process.

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"

EPA's Draft Charge Questions to External Reviewers on the Draft Report: "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water"
September 2017

Introduction

EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate. In January 2017, EPA's contractor (Versar, Inc.) conducted an independent, external, scientific peer review of the draft biologically-based dose-response (BBDR; also known as a PBPK/PD) model and report titled *BBDR Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analyses*. The model predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages and has been revised based on peer reviewer recommendations.

The purpose of this review is to seek guidance from expert peer review on the scientific assessment titled *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (e.g., MCLG Approaches Report) that links the revised perchlorate BBDR model predictions to neurodevelopmental effects to inform decision-making for perchlorate under the Safe Drinking Water Act. The outcome of this peer review is not the derivation of an MCLG; rather, it is to solicit expert comment on the proposed approaches that might be used to inform future decisions on the derivation of an MCLG.

MCLGs are non-enforceable, health-based goals that EPA sets for each regulated drinking water contaminant. In accordance with the Safe Drinking Water Act (SDWA), they are set at a level at which no known or anticipated adverse human health effect occurs and to allow for an adequate margin of safety. MCLGs consider only public health, and not limits of analytical measurement and treatment technology effectiveness. SDWA requires that EPA establish the enforceable Maximum Contaminant Level (MCL) as close as feasible to the MCLG taking costs and benefits into consideration.

Peer Review History

In 2012, as a part of the National Primary Drinking Water Regulation development process for perchlorate and in accordance with the requirements of the SDWA, EPA sought recommendations from EPA's Science Advisory Board (SAB) on approaches to inform the derivation of a perchlorate MCLG.

In 2013, the SAB recommended the following:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling (PBPK);
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode of action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; and
- extend the [BBDR] model expeditiously to...provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages.

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The SAB stated that this data-driven approach represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages than is possible with the default approach for deriving an MCLG, and that EPA should also consider available data on potential adverse health effects (neurodevelopmental outcomes) due to thyroid hormone level perturbations regardless of the cause of those perturbations. See Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate, EPA-SAB-13-004.

Based on the SAB's recommendations, EPA, with contributions from the Food and Drug Administration, developed a BBDR model to predict the effect of perchlorate on the thyroid gland in formula-fed and breast-fed infants, and in lactating women. This draft model was integrated with a previously published model that similarly predicted the effects of perchlorate on serum thyroid hormone concentrations in the 3rd trimester pregnant woman and her fetus. The model was subjected to external peer review in January 2017. The final peer review report titled *External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water* is available through the docket at https://www.regulations.gov/docket?D=EPA-HQ-OW-2016-0439

Revisions to the BBDR Model Following January 2017 Peer Review

EPA considered all of the peer reviewers' recommendations from the January 2017 peer review and focused on those that were anticipated to be most important for increasing the scientific rigor of the model and modeling results. These revisions are summarized in Chapter 3 of the MCLG Approaches Report; additional detail is available in Appendix E. Model revisions focused on the following key recommendations:

- extending the model to early pregnancy;
- incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- conducting an uncertainty analysis for key parameters.

The revised BBDR model does not explicitly address consideration of other goitrogens. Previous peer reviewers (2017) were mixed on their recommendations regarding the issue of consideration of other goitrogens. A recent review of thiocyanate pharmacokinetics and modes of action indicates that an attempt to address other goitrogens in the model would involve significant uncertainty (Willemin & Lumen, 2017). However, it is expected that the model predictions may, in fact, incorporate the effect of perchlorate along with exposure to other goitrogens because the model predictions for zero perchlorate exposure are calibrated to National Health and Nutrition Examination Survey (NHANES) data, which are from a population with an exposure distribution to other goitrogens that is assumed to be independent of perchlorate.

EPA's Approaches for Informing the Derivation of an MCLG

EPA has developed a two-stage approach linking the revised BBDR model results with quantitative information on neurodevelopmental outcomes from epidemiological studies. EPA has also developed an alternative population-based approach that uses the revised BBDR model to evaluate a shift in the population of pregnant women who could be hypothyroxinemic.

The first stage of the two-stage approach is the development of the revised BBDR model that describes thyroidal hormone production in women of childbearing age with low/adequate iodide intake and predicts the relationship between perchlorate exposure and changes in thyroid hormone levels in early

pregnancy. The available data for the second stage of the analysis comes from epidemiological studies that evaluated maternal thyroid hormone levels in early pregnancy and neurodevelopmental outcomes (these are not studies evaluating perchlorate exposure). Based on the recommendations of previous peer review panels, EPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes. For this reason, EPA did not conduct a complete, systematic review of the body of literature on this topic. However, EPA conducted a focused review of the published literature and identified 29 epidemiological studies that examined thyroid hormone levels and neurodevelopmental outcomes. Of these 29 studies, fourteen provide categorical data that assist in understanding the implications of altered thyroid hormones, and fifteen provide more detailed dose-response characterizations via regression analyses to inform the relationship between low thyroid hormone levels and neurodevelopmental effects in offspring.

EPA focused on the latter set of fifteen studies due to their more robust dose-response analyses, which included studies that found statistically significant changes and studies that did not find a statistically significant correlation. Among these studies, the number of subjects ranged from 22 to 3,839. In many of these studies the general outcomes, though not statistically significant showed a positive relationship that was consistent with the studies used for quantitative analyses. In some instances, the studies had results that were negative or inconsistent with the studies that were used for the quantitative analyses. EPA presents and characterizes all of these studies in Chapter 5 of the report.

Five studies in this group of fifteen were identified (Pop et al., 1999; 2003; Finken et al., 2013; Korevaar et al., 2016; and Vermiglio et al., 2004) that included data that were used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy (the focus of the analysis) and changes in neurodevelopment in offspring. Neurodevelopmental outcomes associated with these studies included assessment of Bayley Scales of Infant Development, Weschler Intelligence Scales for Children, a Dutch non-verbal intelligence test (the Snijders-Oomen Niet-Verbale Intelligentie Test) and Standard Deviation of Reaction Time

Using the output from the revised BBDR model (stage 1 of the analysis) and the quantitative relationships between thyroid hormone levels and neurodevelopmental effects from the published epidemiological studies (stage 2 of the analysis), EPA characterized the relationship between perchlorate exposure on fT4 levels in pregnant mothers during early gestation and the potential for changes in neurodevelopmental outcomes in their offspring.

EPA's alternative population-based approach estimates the shift in the population of hypothyroxinemic, pregnant women that would result from perchlorate exposure. EPA used the BBDR model predictions to estimate the proportion of hypothyroxinemic pregnant mothers in the population, assuming a distribution of fT4 levels with a consistent iodide intake.

Charge Questions

Topic #1: General Questions

1. Please comment on the appropriateness of focusing the current evaluation on perchlorate's potential impact on the fetuses of hypothyroxinemic pregnant women during early gestation for the purposes of informing a perchlorate MCLG.

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2. Please identify any additional peer-reviewed studies that could inform the BBDR modeling or the quantitative relationship of thyroid hormone levels to neurodevelopmental outcomes. If an alternative study data set would be more appropriate, please outline how such data might be used.

Topic #2: BBDR Modeling to Predict Changes in Thyroid Hormone Levels in Early Pregnancy

The revised BBDR model seeks to predict the pharmacokinetics and pharmacodynamics of iodide and perchlorate, as well as the thyroid hormones T3 and T4 and TSH, in non-pregnant and pregnant women, including those with low iodide intake, and changes in thyroid hormone levels.

3. Please comment on the assumptions, strengths and limitations of methods for:
    a. the quantitative relationships between oral intake and serum levels of perchlorate during pregnancy under continuous exposure assumptions, and
    b. estimating statistical distributions of specific biochemical parameters that determine serum perchlorate concentrations, urine clearance of iodide and perchlorate, and thyroid iodide uptake for purposes of estimating the effect of environmental levels of perchlorate on maternal fT4 concentrations.
4. Please comment on the assumptions, strengths and limitations of the uncertainty analyses of the parameters.
5. Please comment on the utility of the BBDR model for predicting variability in fT4 levels in the population (e.g., percentiles for different thyroid hormone levels) at varying levels of iodide intake.
6. Please comment on the robustness, precision and sensitivity of the model, and how these factors affect the model's ability to predict changes in fT4 at low perchlorate doses. Consider whether a perchlorate dose range exists for which the modeling predictions would be highly uncertain.
7. The revised BBDR model incorporates a TSH feedback loop defined by an equation from Hadlow et al. (2013) (J Clin Endocrinol Metab, 98(7): 2936-2943), with an adjustment factor to match specific data sets or population percentiles, to describe the relationship between fT4 and TSH.
    a. Please comment on the assumptions, strengths and limitations of this approach to incorporate a TSH feedback loop into the BBDR model.
    b. Noting the reliance on the Hadlow et al. (2013) study, please comment on whether there are other studies that should be considered and describe how they would improve the analysis.
    c. Please comment on the approach for characterizing inter-individual variability in relevant populations from which the epidemiological data were obtained.
8. Since the observational thyroid hormone data that are used to calibrate the model derive from populations exposed to goitrogens other than perchlorate, EPA has made an assumption that the model parameters may implicitly account for exposures to these other goitrogens. As such, the exposure to perchlorate is assumed to be effectively added to this background goitrogen exposure as discussed in Chapter 3.5 of the report.
    a. Please comment on the validity of this assumption and the extent of uncertainty associated with this assumption.

Topic #3: Identification of Published Literature and Quantitative Relationship of Thyroid Hormone Levels to Neurodevelopmental Outcomes

9. EPA identified 15 studies with information that could inform the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes.

    a. Please comment on whether EPA has clearly identified the criteria to identify studies and the adequacy of the strategy for conducting the literature search. Are these criteria scientifically supportable, and did EPA apply them properly?

    b. Please also comment on the summary and characterization of the literature in Chapter 5 of the MCLG Approaches Report and identify any inaccuracies or mischaracterization of the studies.

10. EPA focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, MDI, PDI and reaction time) based on the measurement of fT4 during early pregnancy at week 12, 13 and 16.

    a. Please comment on the assumptions, strengths and limitations of focusing on the five studies and associated neurodevelopmental end points to inform an MCLG, including but not limited to study design, evaluation of neurological endpoints, sample size, iodide nutrition status, potential confounders such as smoking, and study population.
    b. Please comment on whether the chosen studies are sufficiently robust for the purpose of informing the derivation of an MCLG.
    c. Please provide advice on reducing any identified limitations.

11. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes.

    a. Please comment on the assumptions, strengths, and limitations of using the regression analyses to inform the relationship between thyroid hormone levels and neurodevelopmental outcomes.
    b. Please identify additional data or analyses EPA could use to quantify the relationship between thyroid hormone levels and neurodevelopmental effects, including how this information would be expected to improve the analysis.
    c. Please comment on whether there is a magnitude of change in fT4 below which the relationship between fT4 and neurodevelopmental effects should not be used because it is too uncertain.
    d. Please comment on whether other studies that were identified in the literature search (e.g., studies that found effects but lacked statistical significance, studies that did not find an effect, studies that found categorical relationships between fT4 and neurodevelopmental outcomes) could be utilized to quantitatively characterize the relationship between fT4 and neurodevelopmental outcomes or inform uncertainty associated with the analysis presented.

Topic #4: Alternative Population-Based Approach and Comparison to the Two-Stage Approach Linking Thyroid Hormone Levels to Neurodevelopmental Outcomes

12. Please comment on the assumptions, strengths and limitations associated with the population-based approach that is focused on a shift in the proportion of the population that could be considered hypothyroxinemic.

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13. Hypothyroxinemia is the condition of having an abnormally low level of T4 in the blood and TSH is in the normal range, and in diagnosing this condition the threshold for "abnormally low" is often selected to be the 2.5th, 5th or 10th percentile of the population fT4 distribution. Because the BBDR model can be calibrated to any given percentile, but does not predict the distribution of fT4 levels, it was necessary to derive a fT4 distribution to identify a hypothyroxinemic threshold. EPA assumed a lognormal distribution with a Geometric Standard Deviation based on 2 to 3 studies depending on the gestational week. Please comment on the assumptions, strengths and limitations of the derived fT4 distribution for the purposes of this analysis.
14. Please comment on the strengths and limitations of the two-stage approach versus the alternative population-based approach to inform the derivation of an MCLG.
15. Please comment on whether there are better strategies for estimating the potential impact of perchlorate exposure in early pregnancy on neurodevelopmental outcomes that are likely to be more scientifically defensible than the approaches presented. If an alternative approach would be more appropriate, please outline specifically how the approach might be developed given the current available state-of-the-science and data.

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United States
Environmental Protection
Agency

Peer Review Draft: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water – BBDR Modeling

Volume II
Appendix A

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1. 1T BBDR Model Structure and Equations

This appendix describes a biologically-based dose-response (BBDR) model for the uptake and disposition of iodide and perchlorate, and the synthesis and disposition of thyroid hormone parameters in a woman (mother) prior to conception and through gestation week (GW) 16 of pregnancy. For convenience this is called the "1T BBDR Model" herein. The structure of the 1T BBDR Model, shown in Figure A-1 and a list of key model variables is given in Table A-1.

The 1T BBDR Model structure is adapted from the third-trimester model of Lumen, Mattie & Fischer (2013) and the lactation iodide/thyroid hormone model of Fischer et al. (2016), which were adapted in turn from the preceding life-stage perchlorate PBPK model of Clewell et al. (2007). A thorough evaluation of the Clewell et al. (2007) life-stage model was conducted previously by the U.S. EPA (2009) and the model structure and assumptions were determined to be adequate for the purpose of predicting the effect of perchlorate on iodide uptake by the thyroid. Minor corrections of the Clewell et al. (2007) model were brought forward to Lumen et al. (2013) and that model and model code were subjected to a thorough quality assurance review prior to its adaptation into the current model. Therefore, components of the BBDR model that have not been changed from those previous reviews and evaluations, in particular the perchlorate and iodide sub-models, are only described briefly here, and most of the assumptions and choices made in developing those models are not revisited. This document does describe in detail the changes made to adapt the Lumen et al. (2013) model to describe the non-pregnant woman and first trimester of pregnancy.

Table A-1. Key 1T BBDR Model Variables[a]

Variable		DEFINITION
Iodide	**Perchlorate**	
Aplasma_I	Aplasma_P	amount in arterial blood plasma (nmol)
Ca_I	Ca_P	concentration in arterial plasma (nM)
---	Abind_P	amount bound in plasma (nmol)
---	CAbind_p	concentration bound in plasma (nM)
---	ARBC_P	amount in red blood cells (nmol)
---	CRBC_P	concentration in red blood cells (nM)
Arob_I	Arob_P	amount in rest of body (nmol)
Crob_I	Crob_P	concentration in rest of body (nM)
AthyB_I	AthyB_P	amount in thyroid blood (nmol)
CthyB_I	CthyB_P	concentration in thyroid blood (nM)
AthyT_fI	AthyT_P	free (unbound) amount in thyroid tissue (nmol)
CthyT_fI	CthyT_P	free concentration in thyroid tissue (nM)
Abound_I	---	amount of iodide bound in thyroid (tissue) (nmol)
T4 (thyroxine)	**T3 (triiodothyronine)**	
AT4	AT3	total amount in volume of distribution (nmol)
CT4	CT3	total concentration in volume of distribution (nM)
CfT4	CfT3	free concentration (nM)

[a] The model code contains other variables, not listed, such as those used to check conservation of mass. A parallel set of variables to track radio-iodide are also contained in the model.

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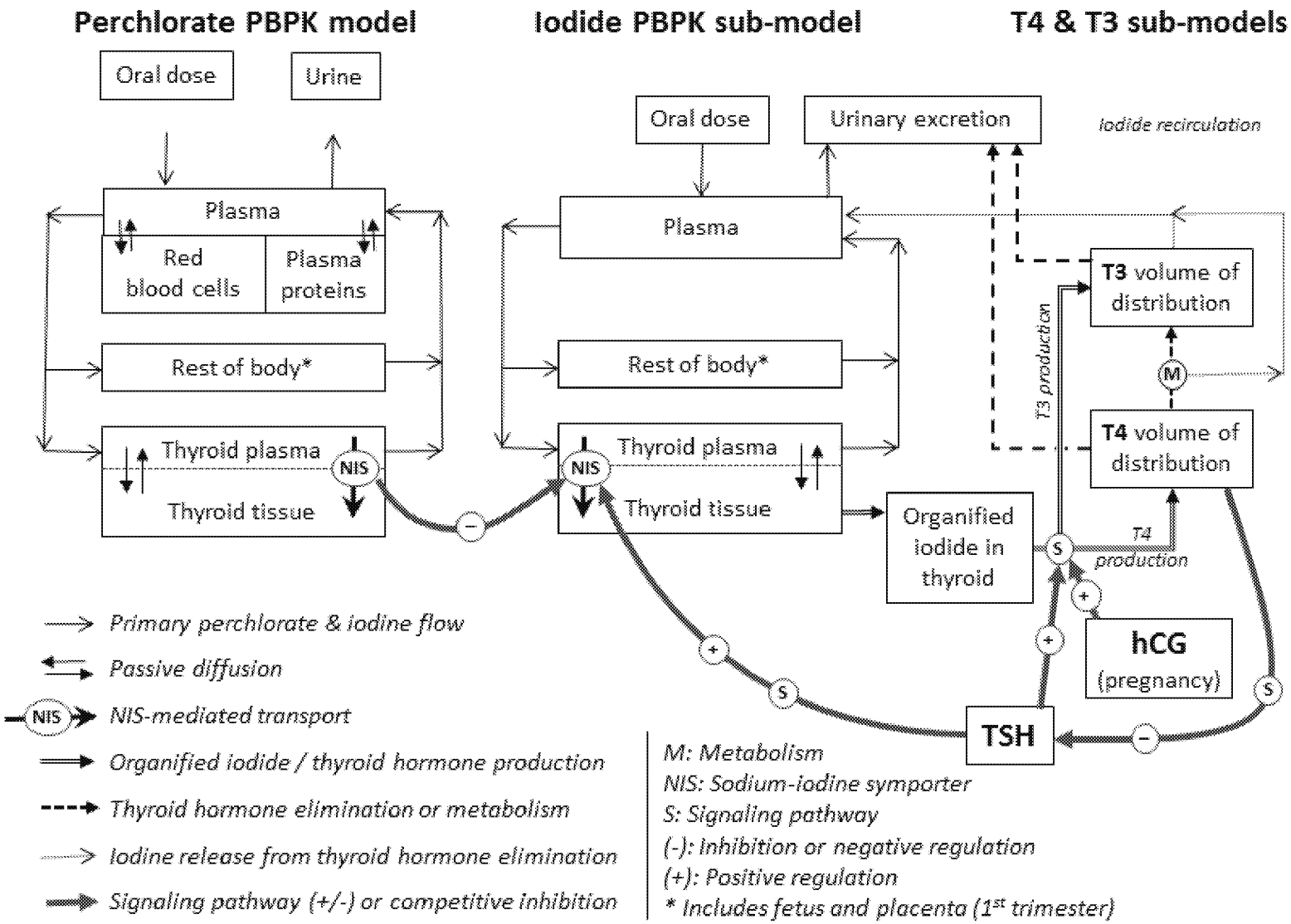
Figure A-1. Overview of the Structure of the Early Pregnancy BBDR Model



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Neurodevelopmental effects have been associated with changes in maternal thyroid hormone (TH) levels (in particular, serum concentrations of free T4 (fT4)) in the first trimester (e.g., Korevaar et al., (2016)). Therefore, the model structure has been refined to focus on predicting maternal TH levels during early pregnancy. The model is designed to simulate conditions in the woman prior to pregnancy, since pre-pregnancy TH and thyroid iodine levels are primary determinants of TH and iodine levels during pregnancy.

The current model significantly simplifies some aspects of the Lumen et al. (2013) model: the maternal body is divided into just two primary compartments, the thyroid and the rest of body (ROB), although partitioning of perchlorate into red blood cells (RBCs) and binding to plasma protein are also included. Because the model is only intended for application prior to and during the first trimester (with calibration data used for up to gestation week 16) when total maternal BW is only expected to increase 3.3% (for a 70 kg woman) and the size of the fetus is expected to be less than 0.15 kg Clewell et al (2007), separate compartments for the fetus and placenta have not been included and are implicitly integrated into the ROB. As gestation progresses, the growing fetus is expected to utilize (metabolize) a more significant fraction of maternally-produced T4 and to utilize iodide as the fetal thyroid grows and becomes functional. If the 1T model failed to adequately account for either of these "sinks", the result would be predicted levels of maternal T4 or fT4 greater than observed – that is, the model would over-predict those levels because a significant sink is left out. Therefore, the adequacy of this assumption has been evaluated by comparing the predicted changes in maternal T4 and fT4 to observational data. If the model over-predicted the data, then the assumption that the fetus and placenta can be lumped into the ROB would be invalidated.

It must also be recognized that adding fetal and placental compartments would more than double the amount of model code that requires QA review, and introduce parameters for fetal processing of iodide, thyroid hormone production, and metabolism at a phase of development when little if any data exist to identify or evaluate these parameters. When the Clewell et al. (2007) perchlorate/radio-iodide PBPK model (which only described the effect of perchlorate on radio-iodide uptake, not hormone production and metabolism) was previously reviewed by the U.S. EPA (2009), model predictions prior to the 3rd trimester were judged too uncertain to use because of the high uncertainty associated with the fetal parameters earlier in gestation. Hence in choosing the 1T model structure it was judged that attempting to include the fetus and placenta would likewise have resulted in insurmountable uncertainty at the cost of significantly higher model complexity and increased likelihood that the model would not be completed in time for application.

To be clear: this model structure simplification is primarily justified because the model only needs to predict maternal TH levels in early pregnancy and the fetus and placenta are assumed to be too small to significantly affect those levels. Even if available, predictions for the fetus would be highly uncertain and there would be no way to quantitatively link them to subsequent health effects. Because some model parameters are calibrated to observed maternal thyroid changes during pregnancy (up to GW 16) and model predictions of maternal thyroid are later shown to match observed values during pregnancy, any error due to this assumption is likely to be minimal.

Model input parameters, those specified as constants input to the mode code, are listed in Table A-2, along with sources for values taken from previous publications. A description of the model structure and equations follows, and then the analyses used to set values for model parameters selected as a part of the 1T BBDR Model development.

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Table A-2. 1T Model Parameter Values, Definitions, and Sources [a]

PARAMETER		DEFINITION
Name	Value (Units)†	
Abndmax0	$17 \cdot 10^6$ (ng) (17 mg)	Maximum capacity for thyroidal bound iodide in the non-pregnant woman (i.e., start of pregnancy); (2.2.2)
AobT4	[-0.07782]‡	2nd order/1st order term for change in fT4:T4 with GW; (1.4.9)
bT4	[0.01845]‡	1st order term for change in fT4:T4 with GW; (1.4.9)
BW0	70 (kg) (default)	Body weight for non-pregnant woman
CLFUI	0.0653 ($L/(h \cdot kg^{0.75})$)	Iodine urinary clearance (scaled, non-pregnant); (1.3.5)
CLFUP	**0.105** [0.122] ($L/(h \cdot kg^{0.75})$)	Perchlorate urinary clearance (scaled, non-pregnant), **2.5th** [50th] percentile of sampling distribution for the median; (1.3.5)
CLUFT3	$2.7 \cdot 10^{-3}$ ($L/(h \cdot kg^{0.75})$)	T3 urinary clearance (scaled, non-pregnant); (Lumen, et al., 2013)
CLUFT4	[$2.83 \cdot 10^{-4}$]‡ ($L/(h \cdot kg^{0.75})$)	T4 urinary clearance (scaled, non-pregnant); (2.2.2)
CT4tar	[99.1]‡ (mIU/L)	"Target" T4 serum concentration, at which TSH feedback term = 1, neither stimulating nor inhibiting hormone production; free T4 target (pM) = CFT4tar = FRT40·CT4TAR·10^3; (2.2.2)
FRT30, FRT40	[$2.77 \cdot 10^{-3}$, $1.03 \cdot 10^{-4}$]‡	Ratio of free to total T3 or T4 (non-pregnant); (2.2.2)
Hct0	0.394	Hematocrit, red blood cell fraction (non-pregnant); (1.4.4)
KBIND_I	[$3.12 \cdot 10^{-3}$]‡ $(nmol \cdot h)^{-1}$	2nd order constant for iodide binding in thyroid; (2.2.2)
KdegT3F	$1.7 \cdot 10^{-4}$ $(h \cdot kg^{0.75})^{-1}$	1st order T3 degradation constant (scaled); (2.2.2)
KdegT4F	$1.9 \cdot 10^{-5}$ $(h \cdot kg^{0.75})^{-1}$	1st order T4 degradation constant (scaled); (2.2.2)
KmNIS_I	3.15×10^4 (nM)	Km for NIS-uptake in thyroid; (Lumen, et al., 2013)
khCG	$3.54 \cdot 10^{-3}$ (L/kIU)	Sensitivity constant for increase in T4 and T3 production per unit hCG (human chorionic gonadotropin); (1.4.12)
KmNIS_P	**489** [732] (nM)	Km for NIS-uptake in thyroid, **2.5th** [50th] percentile of sampling distribution for the median; (1.3.5)
Km_Bp	181 (nM)	Km for perchlorate binding in serum; (Merrill et al., 2005)
KPRODT3F	[$5.83 \cdot 10^{-8}$]‡ $(h \cdot kg^{0.75})^{-1}$	1st order T3 production constant (scaled); (2.2.2)
KPRODT4F	[$6.25 \cdot 10^{-7}$]‡ $(h \cdot kg^{0.75})^{-1}$	1st order T4 production constant (scaled); (2.2.2)
KunbC_P	0.03 ($L/(h \cdot kg^{0.75})$)	1st order constant for unbinding of perchlorate from plasma protein binding (scaled); (U.S. EPA, 2009)
PAthyC_I, PAthyC_P	10^{-4}, 10^{-4} ($L/(h \cdot kg^{0.75})$)	Permeability-area (PA) product for thyroid tissue-plasma (scaled); (Lumen, et al., 2013)
PARBCc_P	10 ($L/(h \cdot kg^{0.75})$)	PA product, red blood cells-plasma (scaled); (U.S. EPA, 2009)
PRBC_P	0.8	Red blood cell: plasma PC for perchlorate; (Clewell, et al., 2007)
Prob_I, Prob_P	0.243, 0.558	Rest of body: plasma PCs for iodide, perchlorate; (1.4.6)
Pthy_I, Pthy_P	0.15, 0.13	Thyroid tissue: plasma PCs; (Merrill, et al., 2005)
pTSH	1	Sensitivity coefficient for TSH feedback regulation; (1.4.13)
QFC0	13.8 ($L/(h \cdot kg^{0.75})$)	Cardiac output constant (scaled, non-pregnant); (1.4.2)
QFthy0	0.015	Fraction of cardiac output going to thyroid (non-pregnant); (Leggett & Williams, 1995), (1.4.5)
TSHtar	[1.37]‡ (mIU/L)	Target TSH level, at which iodine uptake Vmax and thyroid hormone production are at calibrated levels; TSH equation is normalized to yield TSH = TSHtar when CFT4 = CFT4tar; (2.2.2)
VDFT30	0.603 (L/kg)	T3 volume of distribution (non-pregnant); (1.4.7)
VDFT40	0.162 (L/kg)	T4 volume of distribution (non-pregnant); (1.4.7)
VmaxC_Bp	5.9 ($nmol/(h \cdot kg^{0.75})$)	Vmax, perchlorate binding in serum (scaled); (Clewell, et al., 2007)
Table A-6: Key 1T Model Parameters* (cont.)		
VmaxNISF_thy_I	690 ($nmol/(h \cdot kg^{0.75})$)	Vmax, thyroid iodide uptake (scaled, non-pregnant); (1.3.5)
VmaxNISF_thy_P	650 ($nmol/(h \cdot kg^{0.75})$)	Vmax, thyroid perchlorate uptake (scaled, non-pregnant); (Lumen, et al., 2013)
VFpls	0.0539	Fractional volume of blood plasma; (1.4.3)
VFthy	1.34×10^{-4}	Fractional volume of entire thyroid; (1.4.5)

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PARAMETER		DEFINITION
Name	Value (Units)†	
VFthyB	0.276	Fractional volume of thyroid blood; (Lumen, et al., 2013)
VFthyT	0.724	Fractional volume of thyroid tissue; calculated, 1 - VFthyB

[a] Population median values. Parameters for dosing and event timing not included. Citations provided for values taken from previous sources. For all other parameters, numbers in parentheses are Section numbers (internal links) to the sections of this appendix below where values are estimated or their calculation/calibration is described.
† If no units indicated, value is a fraction or a multiplier that has no units.
‡ Parameter is tuned to match observed thyroid hormone levels for an individual or population percentile, hence varies between simulations; value in square brackets is estimate for median of NHANES 2007-12 data.

Additional Considerations in Developing the Pregnancy Model

As previously discussed, hCG is released in the beginning of pregnancy and subsequently increases the amount of T4 in the body. In the model, it is assumed that hCG is only expressed in pregnant women. An empirical function was used to describe hCG for a given gestational age. hCG drives a number of physiological and biochemical changes, but most of these are described by direct empirical fitting of GA-dependent functions to observed data (See Section 1.3). The later include changes in the Vmax for thyroidal NIS and the free:plasma-bound ratios of T3 and T4. However, the rate constants for production of T4 and T3 from bound thyroidal iodide, KprodT4 and KprodT3, are assumed to vary directly as a function of hCG. This function is based on the observed relationship between fT4 and hCG during pregnancy. The relative increase in fT4 versus hCG observed was assumed to also apply to T3 production.

In summary, parameters which change in gestation as an explicit function of hCG or are calculated empirically (not described as a function of hCG) are:

- KprodT4 and KprodT3 (non-pregnant values multiplied by an explicit function of hCG)
- FRconvT4 and FRconvT3 (multiplied by empirical functions of GA)
- VmaxNIS_thy_I and VmaxNIS_thy_P (assumed to vary in proportion; multiplied by an empirical function)

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1.2 Description of BBDR Sub-Models

The 1T BBDR Model can be divided into three sub-models, or components, corresponding to: 1) perchlorate PK and its primary interaction at the NIS; 2) iodide PK and incorporation into thyroidal stores ("binding"); and 3) thyroid hormone and TSH production and regulation. The sections below provide more details on each sub-model, including the mathematical models which are encompassed within the BBDR model.

1.2.1 Perchlorate (and Iodide) Sub-Models

A parallel model structure for perchlorate distribution in the maternal body, plasma, thyroid blood, and thyroid is included in the model. Perchlorate and iodide in the thyroid plasma are assumed to compete for uptake by the sodium-iodine symporter (NIS). In fact, the competitive inhibition of iodine uptake by perchlorate is its presumed mechanism of action.

The perchlorate sub-model also includes binding of perchlorate to plasma binding proteins and distribution of perchlorate between blood plasma and red blood cells (RBCs), as originally described by Clewell et al. (2007). This distribution of perchlorate to multiple subcompartments of the blood was not incorporated into the BBDR model of 2013. Perchlorate binding (but not iodide binding) to serum proteins was then included in the lactation BBDR model developed previously (U.S. EPA, 2016) because the perchlorate sub-model was adapted from Clewell (2007) (as revised by U.S. EPA (2009)) and merged with the iodide lactation BBDR model of Fisher et al. (2013) that also did not include plasma protein binding or distribution into RBCs. That hybrid model structure was used as the starting point for the 1T BBDR model presented here. The perchlorate binding affects the short-term kinetics of perchlorate, but not the long-term average free concentration in the blood plasma which determines its effect on iodide uptake and TH levels. Like perchlorate, plasma protein binding and RBC distribution for iodide does not impact the long-term distribution of iodide to the thyroid and subsequent TH levels. Therefore, the decision made for the 1T BBDR model to not add the corresponding model terms for iodide has little effect on model predictions. It is a modest difference that makes the perchlorate sub-model somewhat more realistic, and that assists in evaluating its behavior against short-term perchlorate PK data. In summary, this discrepancy in model structure (more complex blood compartmentalization for perchlorate vs. none for iodide) exists because it was present in the previous lactation BBDR model (U.S. EPA, 2016) and there was not a compelling reason for altering the corresponding components of the perchlorate or iodide sub-models.

Standard PBPK model equations for flow-limited distribution into the rest of body (ROB) were used for perchlorate and iodide, though as described in the parameter selection section, the partition coefficient was adjusted to account for NIS-facilitated transport of iodide and perchlorate into the skin and mammary gland (where NIS is active). The adjustment assumed that exposure levels were in the linear range (below saturation) for this process, and to account for non-facilitated partitioning into all other tissues.

Exposure to iodine and perchlorate are treated as being delivered directly to the central plasma compartment. Neither is metabolized or otherwise transformed in the GI tract or liver and 100% absorption is assumed for both (Clewell, et al., 2007; Lumen, et al., 2013; Merrill, et al., 2005). Therefore, at steady-state the rate of delivery to the plasma must equal the (average) rate of ingestion. While this simplification in model structure would affect simulations of short-term kinetics, it does not alter the longer-term model predictions.

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1.2.2 Free Thyroidal Iodide and Perchlorate Sub-Models

The total thyroid volume is defined as fraction of body weight (BW), i.e., Vthy = VFthy*BW (L), which is further divided into thyroid tissue and blood, defined as fractions of total thyroid volume: VFthyT (tissue fraction) and VFthyB (blood fraction), respectively. So denoting the BW of the non-pregnant woman to the moment of conception as BW_0, the initial total thyroid volume is:

$$Vthy_0 = VFthy*BW_0 \text{ (L)}$$

and the initial thyroid tissue volume is

$$VthyT_0 = Vthy_0*VFthyT \text{ (L)}.$$

A mass balance on the amount of iodide and perchlorate in the thyroid blood plasma (AthyB_x (nmol), where x is "I" or "P") is determined by mass balance

$$d\ AthyB_x/dt = Qthy*(Ca_x - CthyB_x) - RNISthy_x - RPAthy_x \text{ (nmol/h)},$$

where Qthy is the flow rate of blood plasma to the thyroid (nmol/h), Ca_x is the concentration of x in the arterial blood (nM), CthyB_x is the concentration of x in the thyroid blood (nM), RNISthy_x is the rate of NIS-mediated transport into the thyroid, and RPAthy_x is the rate of passive diffusion into the thyroid. In turn the rate of NIS-mediated transport of x into the thyroid is

$$RNISthy_x = VmaxNIS_thy_x*CthyB_x/[CthyB_x + KmNIS_x*(1 + CthyB_y/KmNIS_y)] \text{ (nmol/h)},$$

where

"y" is the other NIS ligand (e.g., P for perchlorate if "x" is "I" for iodide),

VmaxNIS_thy_x (nmol/h) is the maximum velocity of NIS-mediated uptake for ligand x, and

KmNIS_x (nM) is the saturation constant for NIS-mediated transport of x;

and the rate of passive diffusion of x into the thyroid is

$$RPAthy_x = PAthy_x*(CthyB_x - CthyT_fx/Pthy_x) \text{ (nmol/h)},$$

where

PAthy_x (L/h) is the permeability-area constant for x between the thyroid tissue and plasma

and Pthy_x (no units) is the partition coefficient for x between thyroid tissue and plasma.

1.2.3 Bound (Organified) Thyroidal Iodide Sub-Model*

The amount of iodine that can be stored in the thyroid in organified form (i.e., as a TH precursor) is assumed to have a maximum per unit volume of thyroid tissue, characterized by a calculated model parameter, Cboundmax (nM). To facilitate model calibration, a corresponding input parameter (one

---

* Perchlorate is not bound in the thyroid

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set by the user) is the maximum amount bound in the non-pregnant woman: Abndmax0 (ng). Cboundmax is then calculated as

Cboundmax = Abndmax0/(MWI*VthyT0) = Abndmax0/(MWI*Vthy0*VFthyT) (nM),

where MWI is the molecular weight of iodide.

Given that the thyroid volume changes with pregnancy, it was then assumed that while Cboundmax remains constant, the maximum amount that can be bound is calculated at any given time as

Aboundmax = Cboundmax*VthyT (nmol).

If the amount actually bound at any given moment is Abound_I*, then the amount of unoccupied binding capacity in the thyroid is

Aremain = Aboundmax - Abound_I (nmol).

The rate of iodide binding is then defined as a binary process whose rate depends on the amount of free iodide in the thyroid, AthyT_fI (nmol), the amount of unoccupied binding sites, Aremain, and a binary binding constant, Kbind_I $(nmol*h)^{-1}$:

Rbind_I = AthyT_fI*Aremain*Kbind_I (nmol/h).

When implementing the model in the software, acslX, it was found that if AthyT_fI was calculated as the solution of a typical differential equation, numerical errors occurred for some sets of parameters. This is likely because AthyT_fI is very small (< 0.02% of the total iodide in the thyroid) and equilibrates on a much shorter time-scale than other model variables. Therefore, a pseudo-state-state assumption was made for AthyT_fI; i.e., that the good approximation to the differential equation can be obtained by calculating its value at steady state as a function of the other system variables:

d AthyT_fI/dt = RNISthy_I + RPAthy_I – Rbind_I ≈ 0

= RNISthy_I + PAthy_I*(CthyB_I – CthyT_fI/Pthy_I) - AthyT_fI*Aremain*Kbind_I,

= RNISthy_I + PAthy_I*CthyB_I – AthyT_fI*[PAthy_I /(VthyT*Pthy_I) + Aremain*Kbind_I],

so AthyT_fI ≈ (RNISthy_I + PAthy_I*CthyB_I)/ [PAthy_I /(VthyT*Pthy_I) + Aremain*Kbind_I].

Simulations using this approximation were compared to numerical integration of d AthyT_fI/dt and found to give indistinguishable results when plotted and to impact tabulated model fT4 predictions by less than 1%

Since Aremain approaches zero as the amount bound approaches Aboundmax, the rate of binding can be said to saturate. But the saturation does not occur as a function of the amount (or concentration) of free iodide in the thyroid, but as a function of the integrated (area-under-the-curve) of that amount, since time is required for Aremain to build up.

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* The model also has a parallel set of equations for radio-iodide that can be used to simulate radio-iodide uptake studies. Hence the amount of bound radio-iodide, Abound_rI, is also included in corresponding equations, but is left out of the model presentation here for brevity.

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Finally, the production of the thyroid hormones, T4 and T3, is assumed to be proportional to the amount of thyroidal bound iodide, Abound_I, with respective rate constants, KprodT4 and KprodT3:

RprodT4 = KprodT4*Abound_I (nmol/h)

and RprodT3 = KprodT3*Abound_I (nmol/h).

However, since 4 iodine atoms are required for production of T4 and 3 are required for T3, the rate of use or depletion of bound iodide in the thyroid is the product of these production rates and the corresponding stoichiometric constants:

RioduT4 = 4*KprodT4*Abound_I (nmol/h)

and RioduT3 = 3*KprodT3*Abound_I (nmol/h).

The total rate of iodine usage depends on the total rates of production, determined by the specific values of KprodT4 and KprodT3.

1.2.4 T4 and T3 Sub-Models

The T4 and T3 sub-models effectively assume that their synthesis from bound iodide and release to systemic circulation are simultaneous, as was done by Lumen et al. (2013). The model does not account for metabolic conversion or iodide recycling within the thyroid itself and the remainder of the T4 and T3 sub-models describe their systemic distribution and conversion, characterized using classical PK volumes of distribution, VDT4 and VDT3 (L), respectively. Both T4 and T3 undergo both metabolic degradation (and conversion of T4 to T3) and urinary elimination. Degradation and urinary elimination are treated separately because degradation releases free iodide back into general circulation, while urinary elimination does not.

For T4 the net rate of metabolic degradation and conversion to T3 is characterized by a first-order rate constant, KdegT4 (h^{-1}), so

RdegT4 = KdegT4*AT4 (nmol/h),

where AT4 (nmol) is the total amount of T4 in the body.

As was done by Lumen et al. (2013), it is assumed that ½ of the T4 processed by this path is converted to T3, releasing 1 mol of iodide (net) per mol of T4, so the rate of iodide release from conversion to T3 is 0.5*RdegT4. The other half of T4 metabolically converted is assumed to be converted to rT3, which the model does not track, which is subsequently degraded completely, leading to a net release of 4 mol of iodide per mol of T4 (one being released in the conversion to rT3 and 3 being released when rT3 is degraded). So the rate of iodide release from that process is 4*0.5*RdegT4, leading to a total net rate of deiodination from T4 equal to:

RdeiodT4 = 0.5*(RdegT4 + 4*RdegT4) (nmol/h).

For T3, all metabolic conversion was simply assumed to be degradation, with rate

RdegT3 = KdegT3*AT3 (nmol/h),

so the rate of deiodination (which releases 3 nmol of iodide per nmol of T3) is just

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RdeiodT3 = 3*RdegT3 (nmol/h).

Most of T4 and T3 are assumed to be bound to serum proteins, with the free fraction (ratio of free to total) characterized by the parameters FrconvT4 and FrconvT3 (no units). The fractions free in the non-pregnant woman are denoted FRT40 and FRT30.

Since the Lumen et al. (2013) defined rate constants for urinary clearance, CLT4 and CLT3 (L/h), in terms of the total T4 and T3 concentrations,

CT4 = AT4/VDT4 (nM)

and CT3 = AT3/VDT3 (nM),

but clearance is expected to depend and vary in proportion to the free concentrations,

CfT4 = FronvT4*CT4 (nM)

and CfT3 = FronvT3*CT3 (nM),

the rates of urinary elimination are calculated as

RelimT4 = CLT4*CT4*FrconvT4/FRT40

and RelimT3 = CLT3*CT3*FrconvT3/FRT30.

This form for elimination rates allows them to vary with the free concentrations, but for the values of CLT4 and CLT3 to be comparable if not identical to those determined by Lumen et al. (2013).

The mass balance equations for T4 and T3 are then:

d AT4/dt = RprodT4 – RdegT4 – RelimT4

and d AT3/dt = RprodT3 + 0.5*RdegT4 – RdegT3 – RelimT3,

which includes the assumption that ½ of T4 degradation is conversion to T3.

1.2.5 TSH Feedback

TSH levels are defined using a model variable with the same name (TSH, mIU/L) that is calculated as an algebraic equation of free T4 concentration (CfT4), using an equation adapted from Hadlow et al. (2013), denoted TSHhad(CfT4).

The Vmax values for NIS in the thyroid and rate constants for T4 and T3 production were all assumed to be regulated by TSH, assuming the same regulatory form

$TSHm = (TSH/TSHtar)^{pTSH}$,

where TSHtar is the "target" level of TSH associated with a "target" level of fT4 (CfT4tar), which can then be set to tune the model to the observed levels for a given individual, population median, or other percentile; i.e., the TSH regulation equation is set such that TSHm = 1 when TSH = TSHtar and CfT4 = CfT4tar. In particular, TSHhad(CfT4) is normalized to TSHhad(CfT4tar), and then

TSH = TSHtar*TSHhad(CfT4)/TSHhad(CfT4tar)

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When CfT4 < CfT4tar, TSHhad(CfT4) > TSHhad(CfT4tar) because it is a negative function of CfT4, hence TSH > TSHtar and therefore TSHm > 1, which yields up-regulation.

Likewise, when CfT4 > CfT4tar, TSHhad(CfT4) < TSHhad(CfT4tar), hence TSH < TSHtar, and therefore TSHm < 1, which yields down-regulation.

The coefficient, pTSH, is included in the function for TSHm to allow for tuning of the strength of the TSH feedback, but in practice model simulations versus. data appear quite adequate with pTSH = 1.

In order to run the model with TSH feedback activated for full simulations or inactivated for model calibration, a 0/1 switch, TREG, is also used as a model parameter. The regulatory term for TSH in the model code is then defined as:

$$TSHreg = 1 - TREG + TREG*TSHm = 1 - TREG + TREG*(TSH/TSHtar)^{pTSH},$$

In which case TSHreg is identically 1 when TREG = 0, and equals TSHm when TREG = 1. To be clear, TREG is only set to 0 (TSH signaling turned off) for model calibration. Otherwise TREG = 1 for all model simulations and results, with TSH signaling being continuously operative.

As indicated above, TSHreg multiples both the Vmax for NIS-mediated uptake of iodide (and perchlorate), KprodT4, and KprodT3.

1.3 Probabilistic Parameter Estimation of Key Parameters for a BBDR Model Describing Perchlorate, Iodide, and Thyroid Hormones

1.3.1 Introduction

We determined distributional estimates of four key parameters using a biologically based dose response (BBDR) model for perchlorate and iodide, adapted from a version previously described, with experimental data obtained from human subjects. In particular, we obtained estimates for urinary perchlorate clearance (in L/h/kg$^{0.75}$), urinary iodide clearance (in L/h/kg$^{0.75}$), the Michaelis-Menten saturation concentration (K_m) for perchlorate uptake (in ng/L) and inhibition of iodine uptake by the sodium iodide symporter (NIS) in the thyroid, and the Michaelis-Menten maximum rate ($V_{\max}$) for iodide uptake by the thyroid (in nmol/h). Estimates were obtained by applying Markov chain Monte Carlo (MCMC) methods to experimental data, which included time course observations of serum perchlorate concentrations, perchlorate amounts in urine samples, and radioactive iodine uptake proportions. In this way, we obtained a joint probability distribution for the four physiological parameters for each of 12 female subjects. From these distributions, one can gauge intra-individual uncertainty, inter-individual variability, and overall population-level variability and uncertainty in the parameter values. One can also propagate these parameter distributions through a PBPK model in order to quantify uncertainty and variability in model outputs.

1.3.2 Data Sets

Greer, Goodman, Pleus & Greer (2002) reported the results of experiments in which they administered 0.5, 0.1, and 0.02 mg/kg/d of perchlorate in drinking water for 14 days to 24 euthyroid subjects (4 males and 4 females in each dose group). Blood and urine samples were collected at a "baseline" visit prior to the start of perchlorate dosing, as well as at several times throughout the dosing period and up until the 15th day after perchlorate dosing ended. Additionally, subjects were directed to ingest a radioactive iodine (^{123}I) capsule at 4 times: one before the perchlorate dosing period, two during the dosing period, and one on the 15th day after perchlorate dosing ended.

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Measurements of the proportion of radioactive iodine dose that arrived in the thyroid were observed at 8 and 24 hours after capsule ingestion in each case. Not all data was observed and recorded in all cases. Data availability for the female subjects from the Greer study (Greer, et al., 2002; Greer, Goodman, Pleus, & Greer, 2005; Staff, 2002) is summarized in Table A-3.

The raw data obtained by Greer et al. (2002) were provided to us by Dr. Gay Goodman (coauthor on the study) as Microsoft Excel files with names as listed below:

(1) ***AFRL Serum Perchlorate Data Corrected 2001-12-28a, updated 2017-02-14.xlsx***,
(2) ***AFRL Urine Perchlorate by Event Corrected 2005-07-09.xls***, and
(3) ***Thyroid Uptake Data Final 08-16-00.No Stats.xlsx***.

We used a Python script to read in the raw data, and to process it to create Python data structures containing all the relevant features (column headings) and information (cell entries). As a preliminary step, however, we saved all pertinent worksheets from the above-named Microsoft Excel files as CSV ("comma separated values" format) files. The names of the resulting CSV files are listed in Table A-4.

Table A-3. Data Availability and Prior Refinement[a]

Subject	Dose (mg/kg/d)	Age (years)	Body Mass (kg)	SPC	UPA	RIU	Prior
AN	0.5	22	72.0	Yes	Yes	Yes	1
CW	0.5	45	100.5	Yes	Yes	Yes	1
AB1	0.5	26	54.2	Yes	Yes	Yes	1
RC	0.5	43	63.2	Yes	Yes	Yes	1
RT	0.1	53	74.6	Yes	No	Yes	2
JF	0.1	44	67.5	Yes	Yes	Yes	2
AH	0.1	25	65.9	Yes	Yes	Yes	2
SG	0.1	52	106.0	Yes	Yes	Yes	2
CB	0.02	34	72.7	Yes (all 4 QD)	Yes	Yes	3
SV	0.02	49	67.0	No	No	Yes	3
SK	0.02	49	61.2	Yes (3 > LOD)	No	Yes	3
DC	0.02	52	79.8	No	No	Yes	3

[a] Each subject from the study of Greer et al. (2002) is identified using a two-letter code in the first column. The perchlorate dose level, age, and body mass are provided in the second through fourth columns. Information concerning the availability of serum perchlorate concentration ("SPC"), urine perchlorate amount ("UPA"), and radio-iodide uptake ("RIU") are provided in the next three columns. For each subject, a code that identifies the prior used for parameter estimations is provided in the rightmost column.

Table A-4. Names of CSV files created from raw Microsoft Excel files containing data from the study of Greer et al. (2002)[a]

Raw Data File	Worksheet Name	CSV File Name
(1)	High dose data	greer_serum_perchlorate_high_dose.csv

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(1)	Mid-dose data	greer_serum_perchlorate_mid_dose.csv
(1)	Low-dose data	greer_serum_perchlorate_low_dose.csv
(2)	Data	greer_urine_perchlorate.csv
(3)	Data	greer_thyroid_raiu.csv

[a] The names of the files containing the raw Excel worksheets are indicated by (1), (2), and (3) in this table, but the actual file names (some of which are quite long) are given in Section 1.3.2 of this report. Certain worksheets within those files, which are named in the middle column were converted into CSV files with the names provided in the final column.

The Python script that processes the CSV files is contained in the file ***read_greer_data.py***. This script reads in each of the CSV files named in Table A-4 and creates and saves a data frame for each dose group and data type as follows:

(1) greer_serum_perchlorate_high_dose_df,
(2) greer_serum_perchlorate_mid_dose_df,
(3) greer_serum_perchlorate_low_dose_df,
(4) greer_urine_perchlorate_high_dose_df,
(5) greer_urine_perchlorate_mid_dose_df,
(6) greer_urine_perchlorate_low_dose_df,
(7) greer_thyroid_raiu_high_dose_df,
(8) greer_thyroid_raiu_mid_dose_df, and
(9) greer_thyroid_raiu_low_dose_df.

The script that creates these data frames ensures that consistent column (feature) names and consistent formatting conventions (e.g., all capital letters for subject codes) are used for all data. The script also converts date and time information for each observation into an "Experimental Time" that corresponds to the number of hours elapsed since 00:00:00 on "Experimental Day 1" for each of the subjects. The script contained in ***read_greer_data.py*** saves these data frames in CSV format so that they can be read and utilized by other scripts. The files containing the data frames have the same names provided in the foregoing numbered list except that ".csv" is appended in each case (e.g., the first data frame from the list is saved as ***greer_serum_perchlorate_high_dose_df.csv***).

1.3.3 Mathematical Models

The model used for parameter estimation was adapted from the lactating mother model described previously in the perchlorate BBDR model draft technical report (U.S. EPA, 2016). In the adapted model, which was implemented using R and MCSim, lactation is eliminated and simulations of exposure scenarios set exposures to begin 200 days after childbirth. This time was chosen because in the lactating (postpartum) mother model the mother's body mass decreases up until 180 days after childbirth and we assume that steady state conditions in maternal tissues have been reached after 200 days. Eliminating lactation and beginning exposures at 200 days ensures that the model more accurately represents a non-pregnant adult woman.

In addition to the modifications described above, logic was added to the model to allow for dosing regimens that match experimental conditions described in a human study (Greer, et al., 2002). In particular, the modified model allows for simulations in which doses of perchlorate and radioactive iodide can be added to a stomach compartment at specified times during the simulation. Furthermore, compartments (and corresponding state variables and differential equations) describing radioactive

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iodide were incorporated into the model. Thus, while the adapted model takes into account similarities and interactions between dietary (non-radioactive) iodide and radioactive iodide, it generates time-course information regarding the kinetics for each form of iodide separately.

The first trimester BBDR model described elsewhere in this report was not used for estimation of the four physiological parameters named in Section 1.3.1, as the Bayesian parameter estimation efforts described here and the development of the first trimester BBDR model were conducted in parallel (during the same time frame). Nevertheless, it is assumed that the specific parameter values estimated using the adapted "non-lactating mother" model described above can be directly applied or easily translated for use in the first trimester BBDR model. (In the first trimester BBDR model, parameter values affected by pregnancy-induced physiological changes are extrapolated from non-pregnant values such as those estimated here.) Simulations were conducted with the first trimester model using the parameters estimated in this analysis to confirm that the perchlorate PK data from Greer et al. (2002) are reproduced with that version of the model.

1.3.4 Parameter Estimation Methods

Our basic method involved applying Bayes' Theorem for inverse problems in order to obtain distributional estimates of four parameters in a BBDR model for perchlorate and iodide by comparing model outputs with data from the Greer et al (2002) study. Bayes' Theorem for inverse problems (Smith, 2014) can be stated as

$$\pi(\theta|\mathcal{D}) = \frac{\pi(\mathcal{D}|\theta)\cdot\pi_0(\theta)}{\int_{\mathbb{R}^p}\pi(\mathcal{D}|\vartheta)\cdot\pi_0(\vartheta)\,d\vartheta} = \frac{\mathcal{L}(\theta;\,\mathcal{D})\cdot\pi_0(\theta)}{\int_{\mathbb{R}^p}\mathcal{L}(\vartheta;\,\mathcal{D})\cdot\pi_0(\vartheta)\,d\vartheta},$$

where $\pi(\theta|\mathcal{D})$ is the posterior probability density of the parameters θ given the data $\mathcal{D}$, $\mathcal{L}(\theta;\,\mathcal{D}) = \pi(\mathcal{D}|\theta)$ is the likelihood function that describes the relative likelihood of the parameters θ given the data $\mathcal{D}$, $\pi_0(\theta)$ is the prior probability density of the parameters, p is the number of parameters in the vector $\theta \in \mathbb{R}^p$.

In constructing our likelihood function, we assume that the errors (differences between model predictions and observed data) are normally distributed. Thus, we make frequent use of the probability density function for a normally distributed random variable $X \sim N(\mu, \sigma)$ in the discussion below. This density function is given by

$$f_X(x;\mu,\sigma) = (2\pi\sigma^2)^{-1/2}\cdot\exp\left[\frac{-(x-\mu)^2}{2\sigma^2}\right],$$

where x denotes the observed value of the random variable X, and μ and σ denote the mean and standard deviation, respectively, of the normal distribution describing this random variable.

To begin with a simple example, one could construct the likelihood function for $\theta = (\mu, \sigma)$ given data $\{x_i\}_{i=1}^n$ that consist observations of a normally distributed random variable $X \sim N(\mu, \sigma)$ as

$$\mathcal{L}(\theta;\,\{x_i\}_{i=1}^n) = \prod_{i=1}^{n} f_X(x_i;u,\sigma)$$

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$$= (2\pi\sigma^2)^{-n/2} \cdot \prod_{i=1}^{n} \exp\left[\frac{-(x_i-\mu)^2}{2\sigma^2}\right].$$

One complication that arises in the Greer data is that some observations of serum perchlorate concentrations are recorded as "not detected" when they fall below the limit of detection (0.005 mg/L). Such observations are assigned values equal to one half the limit of detection. This is an example of a "censored" data set (Gelman et al., 2014). The likelihood function for $\theta = (\mu, \sigma)$ given *censored* data $\{x_i\}_{i=1}^n$ with limit of detection x_{lod} is given by

$$\mathcal{L}(\theta;\ \{x_i\}_{i=1}^n) = \prod_{i=1}^{n} \tilde{f}_X(x_i; u, \sigma, x_{\text{lod}})$$

where

$$\tilde{f}_X(x; \mu, \sigma, x_{\text{lod}}) = \begin{cases} f_X(x_i; u, \sigma) & \text{for } x_i > x_{\text{lod}} \\ \int_{-\infty}^{x_{\text{lod}}} f_X(x; u, \sigma)\ dx & \text{for } x_i \le x_{\text{lod}}. \end{cases}$$

Now, suppose we have data consisting of ordered pairs $\{(t_i, y_i)\}_{i=1}^n$, where each t_i is an observation time and each y_i is a quantity observed at the corresponding observation time. Also, assume that there exists a mathematical model y with p parameters given by the vector $q = (q_1, \dots, q_p)$ and that this model produces the expected value of the observed quantity at time t as $y(t, q)$. Finally assume that the observed errors $\varepsilon_i = y_i - y(t_i, q)$ are realizations of independent and identically distributed random variables $\epsilon_i \sim N(0, \sigma)$. Then the likelihood function for $\theta = (q_1, \dots, q_p, \sigma)$ given the data $\mathcal{D} = \{(t_i, y_i)\}_{i=1}^n$ is given by:

$$\begin{aligned} \mathcal{L}(\theta;\ \mathcal{D}) &= \prod_{i=1}^{n} f_X(y_i - y(t_i, q); 0, \sigma) \\ &= \prod_{i=1}^{n} f_X(y_i;\ y(t_i, q), \sigma) \end{aligned}$$

Recall that the data collected in the study of Greer et al. (2002) actually consist of three types time-course observations: serum perchlorate concentrations, urine perchlorate amounts, and radioactive iodine uptake proportions. Thus, the data can be represented as the three sets of ordered pairs $\{(t_i^{\text{spc}}, y_i^{\text{spc}})\}_{i=1}^{n_{\text{spc}}}$, $\{(t_i^{\text{upa}}, y_i^{\text{upa}})\}_{i=1}^{n_{\text{upa}}}$, and $\{(t_i^{\text{riu}}, y_i^{\text{riu}})\}_{i=1}^{n_{\text{riu}}}$, where the symbols spc, upa, and riu indicate data that pertain to serum perchlorate concentrations, urine perchlorate amounts, or radioactive iodine uptake proportions, respectively. Serum perchlorate concentrations $\{y_i^{\text{spc}}\}$ have a limit of detection of $y_{\text{lod}}^{\text{spc}} = 0.005$ mg/L. Our model y with four parameters given by $q = (q_1, q_2, q_3, q_4)$ = (CLUC_P, CLUC_I, KM_TPNG, VMAXTHYC_I) has outputs given by $y^{\text{spc}}(t, q)$, $y^{\text{upa}}(t, q)$, and $y^{\text{riu}}(t, q)$ that correspond to the three types of observations just described. We assume that the errors for each distinct type of observation are independent and identically distributed, so we require a distinct variance parameter for each type of observation. We denote these "nuisance parameters" σ_{spc}, σ_{upa}, and σ_{riu}. Thus, our likelihood function for $\theta = (q_1, q_2, q_3, q_4, \sigma_{\text{spc}}, \sigma_{\text{upa}}, \sigma_{\text{riu}})$ given the data $\mathcal{D} = \left\{\{(t_i^{\text{spc}}, y_i^{\text{spc}})\}_{i=1}^{n_{\text{spc}}}, \{(t_i^{\text{upa}}, y_i^{\text{upa}})\}_{i=1}^{n_{\text{upa}}}, \{(t_i^{\text{riu}}, y_i^{\text{riu}})\}_{i=1}^{n_{\text{riu}}}\right\}$ is given by

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$$\mathcal{L}(\theta;\, \mathcal{D}) = \prod_{i=1}^{n_{\text{spc}}} \tilde{f}_X(y_i^{\text{spc}}; y^{\text{spc}}(t_i^{\text{spc}}, q), \sigma_{\text{spc}}, y_{\text{lod}}^{\text{spc}}) \cdot \prod_{i=1}^{n_{\text{upa}}} f_X(y_i^{\text{upa}}; y^{\text{upa}}(t_i^{\text{upa}}, q), \sigma_{\text{upa}}) \cdot \prod_{i=1}^{n_{\text{riu}}} f_X(y_i^{\text{riu}}; y^{\text{riu}}(t_i^{\text{riu}}, q), \sigma_{\text{riu}}).$$

For the subject RT, who had no urine perchlorate data, we omitted the second term in the right-hand side of this expression – that is, we omitted the contribution of urine perchlorate data to the likelihood function. Similarly, for all subjects in the low-dose group, we omitted the first two terms in right-hand side of this expression because of missing or low-quality data (cf.Table A-3).
We have now explicitly defined the likelihood function we used, but to apply Bayes Theorem for inverse problems, we also require a prior probability density function. For the prior, we assume the parameters in θ are independent of one another and define prior probability density functions for each of these parameters as follows:

$$\pi_0^{q_1}(x) = \begin{cases} 1 & \text{for } 0 < x \leq 10 \\ 0 & \text{otherwise}, \end{cases}$$

$$\pi_0^{q_2}(x) = \begin{cases} f_X(x; 1.863, 0.763) & \text{for } 0 < x \leq 1.863 + 3 \times 0.763 \\ 0 & \text{otherwise}, \end{cases}$$

$$\pi_0^{q_3}(x) = \begin{cases} 1 & \text{for } 6.0 \times 10^3 < x \leq 6.0 \times 10^5 \\ 0 & \text{otherwise}, \end{cases}$$

$$\pi_0^{q_4}(x) = \begin{cases} 1 & \text{for } 1.0 \times 10^3 < x \leq 1.0 \times 10^5 \\ 0 & \text{otherwise}, \end{cases}$$

$$\pi_0^{\sigma_{\text{spc}}}(x) = \begin{cases} 1/x & \text{for } x > 0 \\ 0 & \text{otherwise}, \end{cases}$$

$$\pi_0^{\sigma_{\text{upa}}}(x) = \begin{cases} 1/x & \text{for } x > 0 \\ 0 & \text{otherwise}, \end{cases}$$

$$\pi_0^{\sigma_{\text{riu}}}(x) = \begin{cases} 1/x & \text{for } x > 0 \\ 0 & \text{otherwise}. \end{cases}$$

All of these prior density functions are improper in the sense that they do not integrate to 1. The priors for q_1, q_3, and q_4 are non-informative "flat" priors that contain reference values for the respective parameters – 0.125 L/h/kg$^{0.75}$, 6.0 × 10^4 ng/L, and 4.0 × 10^4 nmol/h – in their domains of support. The prior for q_2 is a normal distribution based upon renal iodine clearance data measured for 13 non-pregnant subjects and reported in Table 2 of Aboul-Khair, Crooks, Turnbull, & Hytten (1964). We applied a Shapiro-Wilk test for normality to these data and concluded that there is not sufficient evidence to reject the hypothesis that the clearance values come from a normal distribution (p = 0.867). Applying the same test, we concluded that there is sufficient evidence to reject the hypothesis that the clearance values come from a lognormal distribution (p = 0.001547). We therefore used maximum likelihood methods to estimate the mean (1.863) and standard deviation (0.763) of the normal distribution describing the clearance data. Since clearance values cannot be negative, we truncated this normal distribution at zero on the left. We also truncated the distribution at 3 standard

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deviations above the mean on the right to develop a prior with finite support that we believe to contain most feasible values for q_2 = CLUC_I, the urinary iodine clearance parameter. A Python script that performs all of these calculations is provided as ***iodide_clearance_prior.py***. For the last three priors, which describe the nuisance standard deviation parameters σ_{spc}, σ_{upa}, and σ_{riu}, we used the Jeffreys prior (Gelman, et al., 2014) for the standard deviation of a normal distribution.

Because the quantity and quality of the data tend to be less for the mid- and low-dose groups (with more missing data, more values that are not detected, and lower signal-to-noise) than for the high-dose group, we began by estimating the posterior distribution of the four parameters for the high-dose group subjects and then adjusted the priors to estimate the posterior distribution of the same parameters for the mid- and low-dose group subjects. The actual prior distributions used to estimate posterior parameter distributions for each subject are indicated by the numbers in the rightmost column of Table A-3. The procedures used to construct these numbered priors are defined below.

1. Use a joint prior distribution (π_0) computed as the product of the independent prior distributions listed above for each of the seven parameters.

2. Obtain samples from the marginal posterior distributions for q_1 and q_2 (CLUC_P and CLUC_I) for the high-dose subjects (AN, CW, AB1, and RC). Use maximum likelihood estimation to find location and scale parameters for a lognormal distribution that best fits the combined posterior samples (from four subjects) of CLUC_P. Replace the prior distribution $\pi_0^{q_1}$ with this lognormal distribution. Similarly replace $\pi_0^{q_2}$ with a best fit lognormal distribution for the combined posterior samples of CLUC_I. Finally, use the joint prior distribution computed as the product of the independent prior distributions as before.

3. Obtain samples from the marginal posterior distributions for q_1 and q_2 (CLUC_P and CLUC_I) for the mid-dose subjects (RT, JF, AH, and SG). Use maximum likelihood estimation to find location and scale parameters for a lognormal distribution that best fits the combined posterior samples (from the four high-dose subjects and the four mid-dose subjects) of CLUC_P. Replace the prior distribution $\pi_0^{q_1}$ with this lognormal distribution. Similarly replace $\pi_0^{q_2}$ with a best fit lognormal distribution for the combined posterior samples (for eight subjects) of CLUC_I.

4. Next, obtain samples from the marginal posterior distribution for q_3 (KM_TPNG) for the mid-dose subjects (RT, JF, AH, and SG). Use maximum likelihood estimation to find location and scale parameters for a lognormal distribution that best fits the combined posterior samples (from just the four mid-dose subjects) of KM_TPNG. Replace the prior distribution $\pi_0^{q_3}$ with this lognormal distribution. Finally, use the joint prior distribution computed as the product of the independent prior distributions as before.

Rather than evaluating the expression given above for Bayes' Theorem for inverse problems, which would require the computationally intensive evaluation of a multidimensional integral, we obtained samples from the posterior distribution of θ (the parameter vector) by applying Markov chain Monte Carlo (MCMC) sampling (Gelman, et al., 2014). Specifically, we used the affine-invariant MCMC ensemble sampler of Goodman & Weare (2010) as implemented in the Python package "emcee" (Foreman-Mackey, Hogg, Lang, & Goodman, 2013). This required us to write a Python function that returns a value proportional to the logarithm of the posterior density. Thus, we constructed a function that computes and returns the value of $\log(\mathcal{L}(\theta;\ \mathcal{D})) + \log(\pi_0(\theta))$, where $\mathcal{L}(\theta;\ \mathcal{D})$ and $\pi_0(\theta)$ are the

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likelihood function and (improper) prior density function already described. This function is defined (with the name "log_posterior") in the Python script contained in the files ***parameter_est_greer_data_high_dose.py***, ***param_est_greer_data_mid_dose.py***, and ***param_est_greer_data_low_dose.py***.

Having defined the likelihood and prior functions, and having imported the data as described, we applied MCMC to estimate the joint posterior distribution of the parameters for each subject. This was performed by calling the "sample" method of the "EnsembleSampler" class from the emcee package (Foreman-Mackey, et al., 2013). This method allows one to produce multiple Markov chains by setting the number of "walkers" (Markov chain generators) to an integer greater than one. For our purposes, we began by generating 100 Markov chains of 3000 iterations (or steps) each. We then computed the potential scale reduction factor (Gelman, et al., 2014), which is an estimate of the factor by which the scale of the current distribution (after 3000 steps) might be reduced if the lengths of the chains were increased indefinitely by continuing for an infinite number of iterations. This "potential scale reduction factor" or PSRF was computed for each parameter for each subject. Values of the PSRF near 1 indicate that chains have converged, and Gelman et al. (2014) suggest using 1.1 as a threshold. For those subjects in which the PSRF for all 7 parameters was less than 1.1 after 3000 iterations, we considered the chains to have converged and combined the last 1500 iterations from each of the 100 chains to form samples of the joint posterior distribution of the parameters. For those subjects in which the PSRF for at least one of the 7 parameters was greater than 1.1 after 3000 iterations, we extended the chains (by continuing the MCMC process) until all PSRFs were less than 1.1. We then considered the chains to have converged and combined the last 50% of the iterations for each of the 100 chains to form samples of the joint posterior distribution of the parameters.

For each subject and each parameter, we also computed the PSRF at intermediate points (once every 200 steps) to provide evidence of improvement (decrease) in the PSRF for longer chains. Plots showing the PSRF versus number of steps in each chain are shown in Figure A-2 through Figure A-7.

After obtaining converged MCMC chains for all parameters for all 12 female subjects, we constructed distributional estimates of the population median values for the four parameters of interest. Here we assume that the 12 female subjects in the Greer et al. (2002) study can be considered to be a representative sample of the adult human female population of the U.S. We acknowledge that this assumption is difficult to support based on the limited demographic information made available by Greer et al., and we also acknowledge that the sample size (12 female subjects) is quite small; nevertheless, this data set Greer et al. (2002) appears to be the most informative controlled perchlorate dosing data set for human subjects that is available. Our strategy for estimating population variability in the median values for each of the four biochemical parameters was as follows:

1. Randomly select 12 subjects (with replacement) from the 12 female subjects from the Greer et al. (2002) study.
2. For each of the subjects from Step 1, select one set of parameter values from the joint posterior distribution by randomly selecting one sample point.
3. For each of the four biochemical parameters, compute the median of the values produced in Step 2.

We repeated this process 100,000 times in order to obtain a sample of the median values for each parameter.

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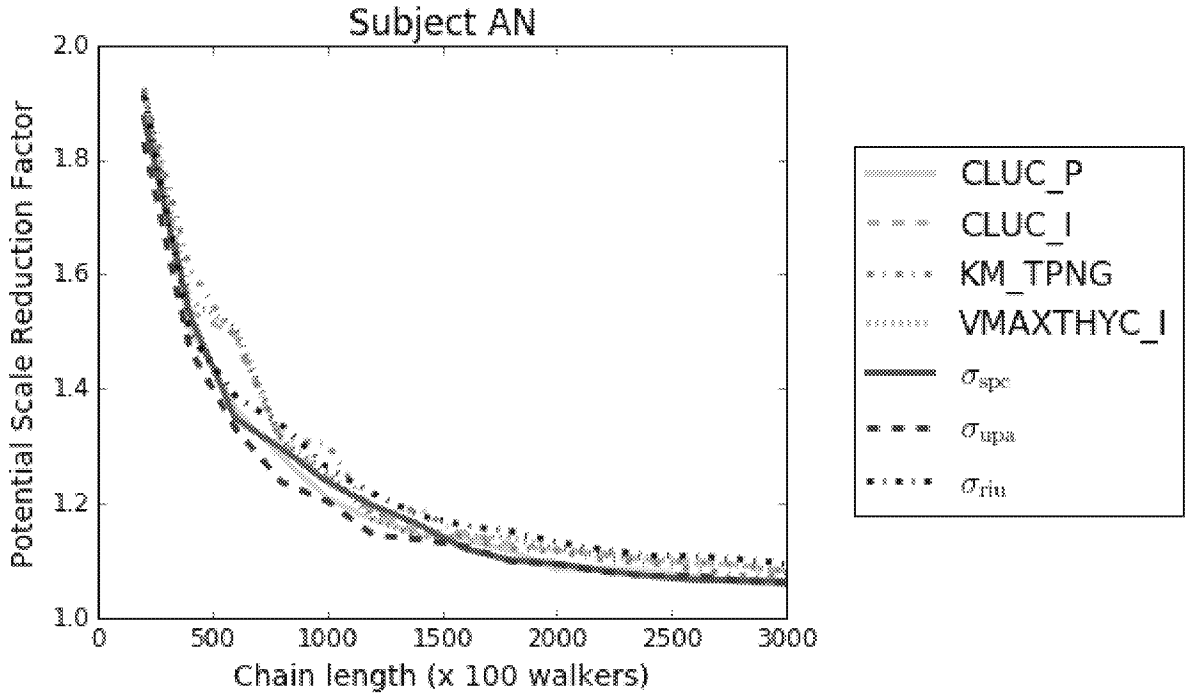
Figure A-2. Plot of the potential scale reduction factor (PSRF) versus the number of steps in each chain for subject "AN" and "CW"



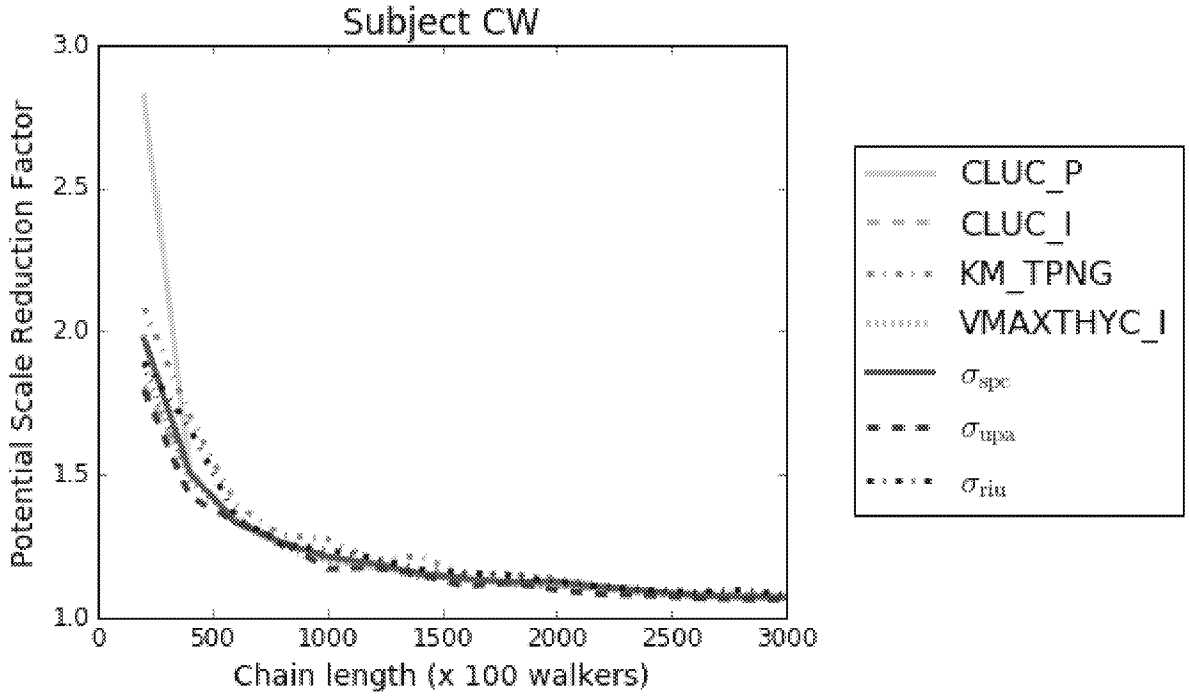


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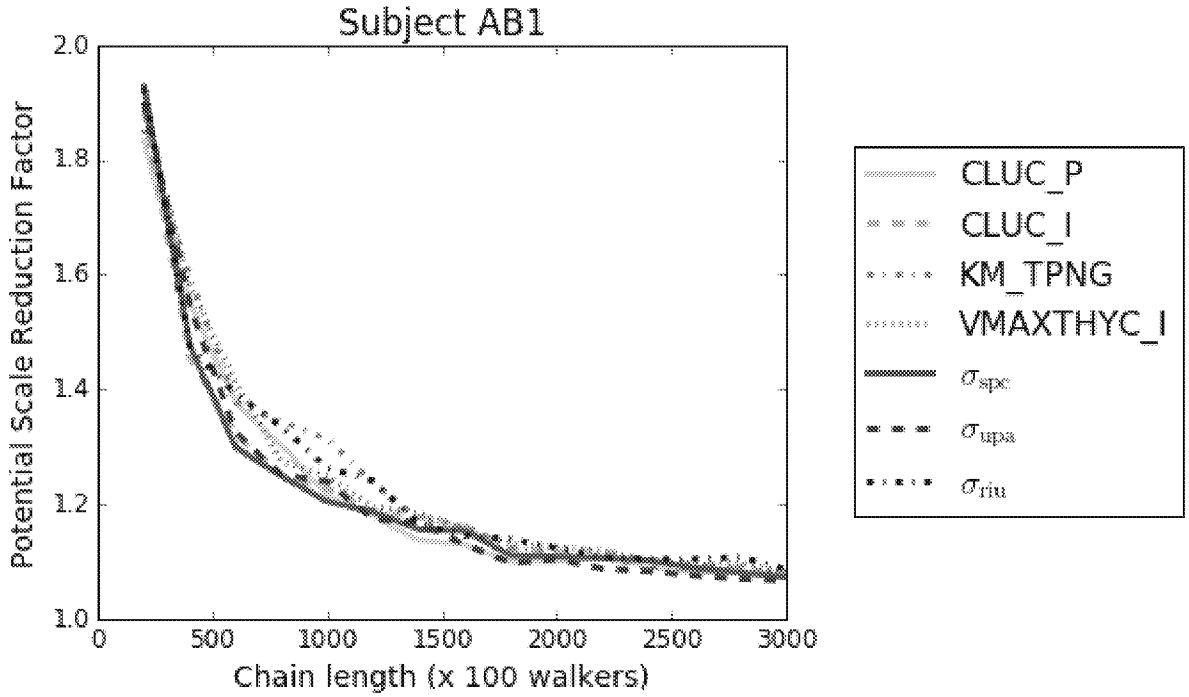
Figure A-3. Plot of the PSRF vs. the number of steps in each chain for subjects "AB1" and "RC"



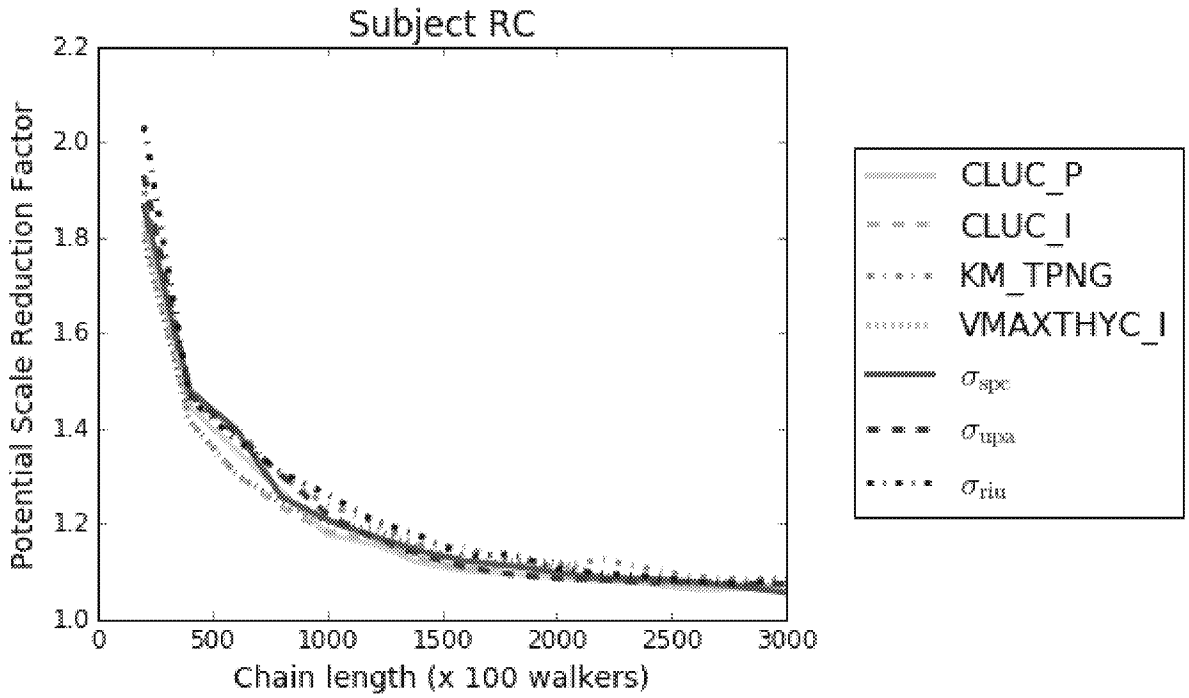


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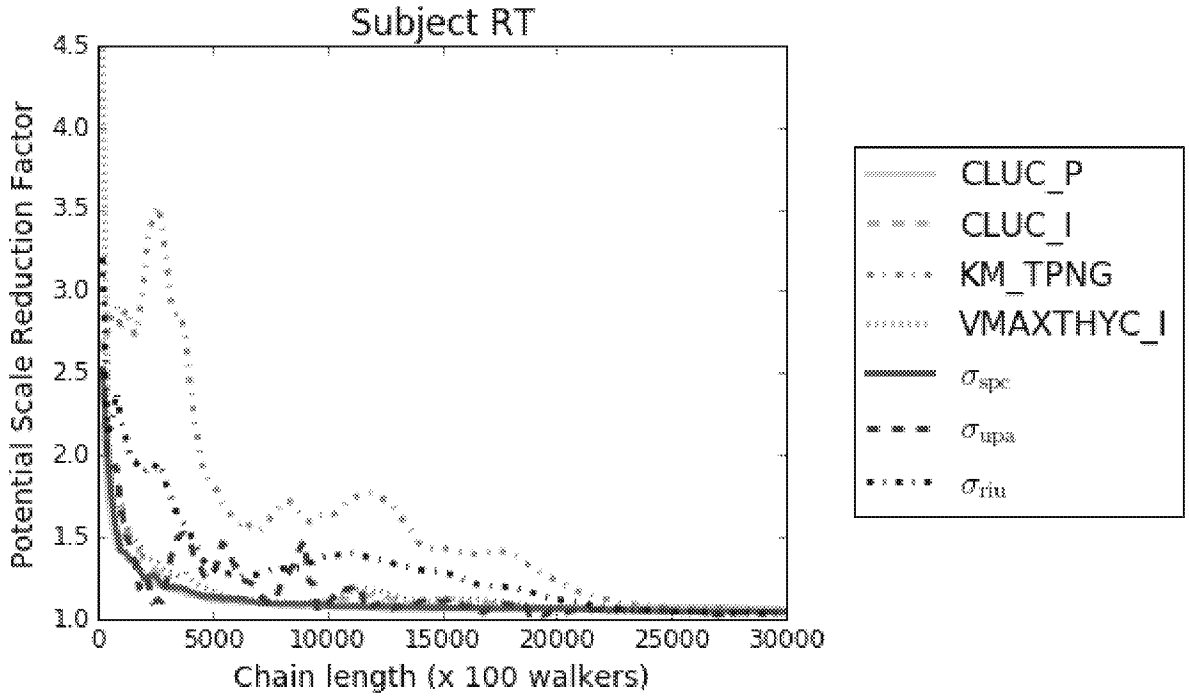
Figure A-4. Plot of the PSRF vs. the number of steps in each chain for subjects "RT" and "JF"



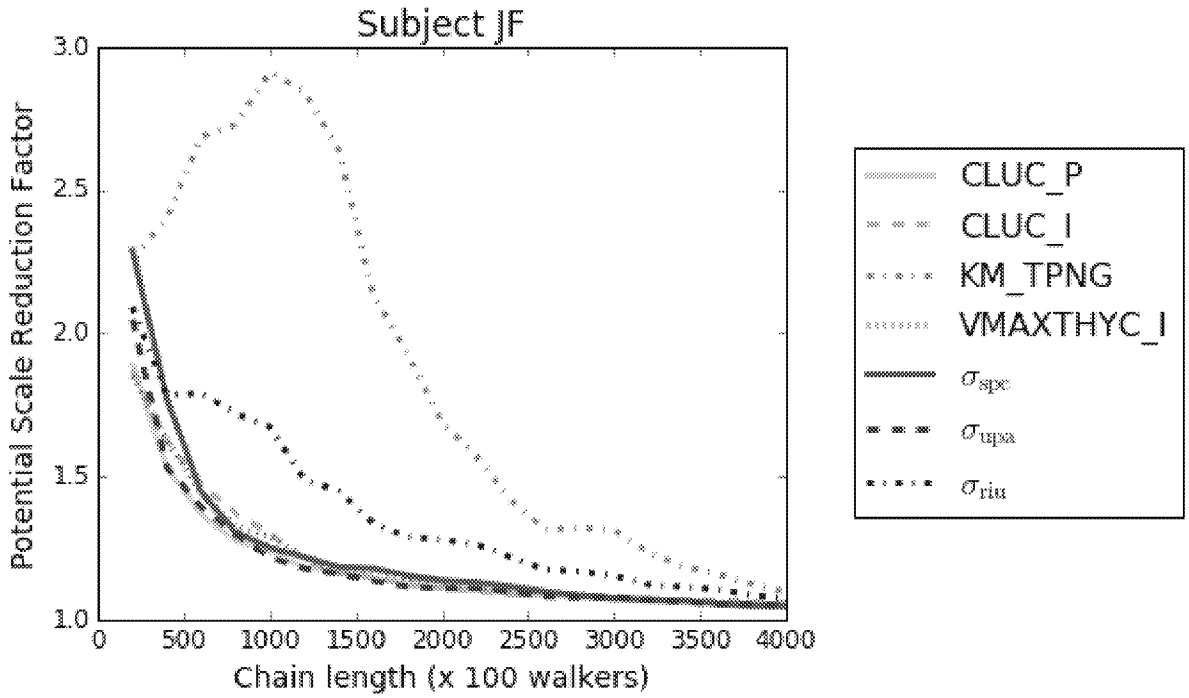


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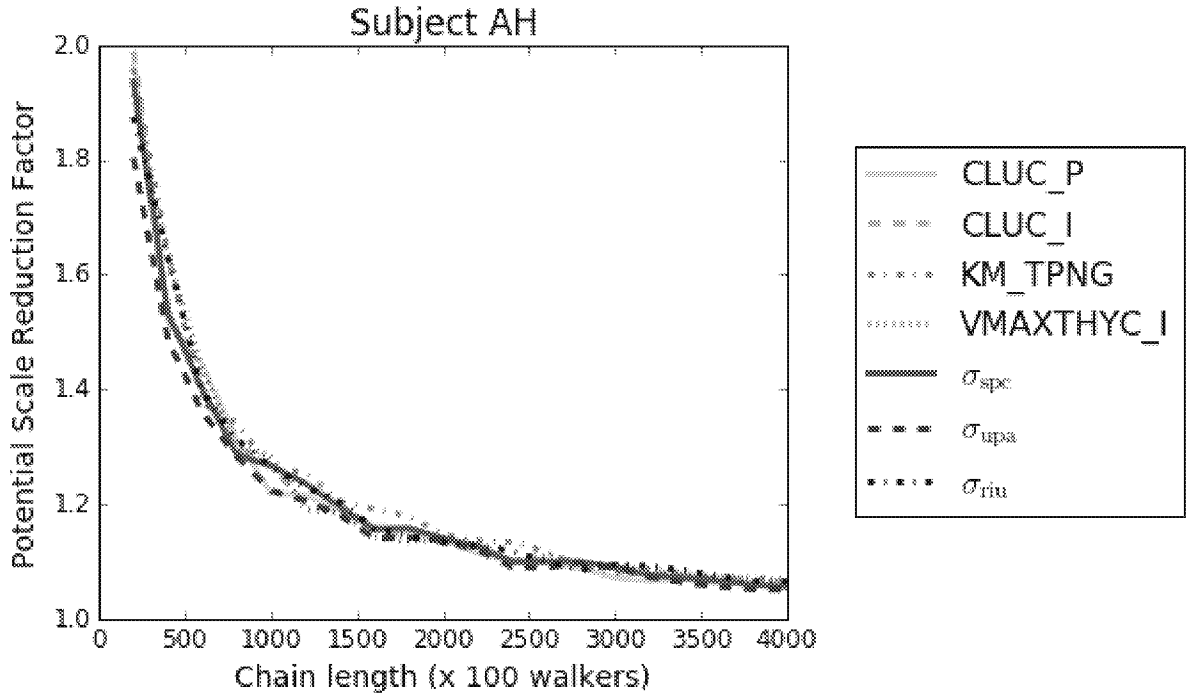
Figure A-5. Plot of the PSRF vs. the number of steps in each chain for subjects "AH" and "SG"



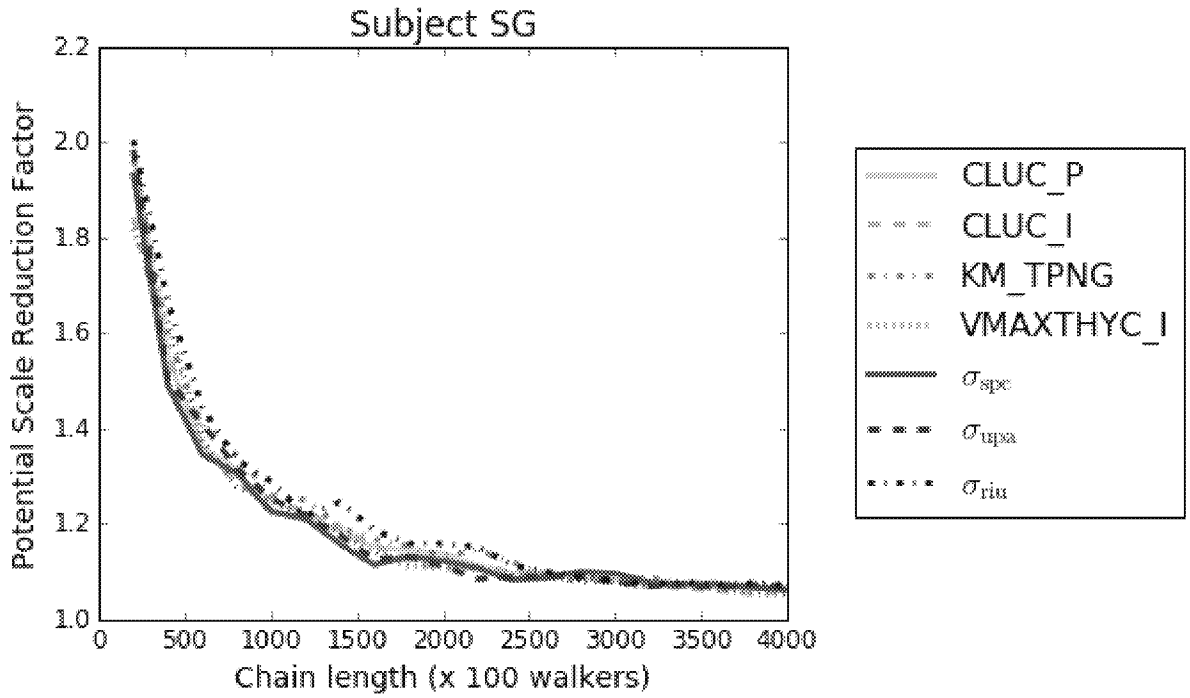


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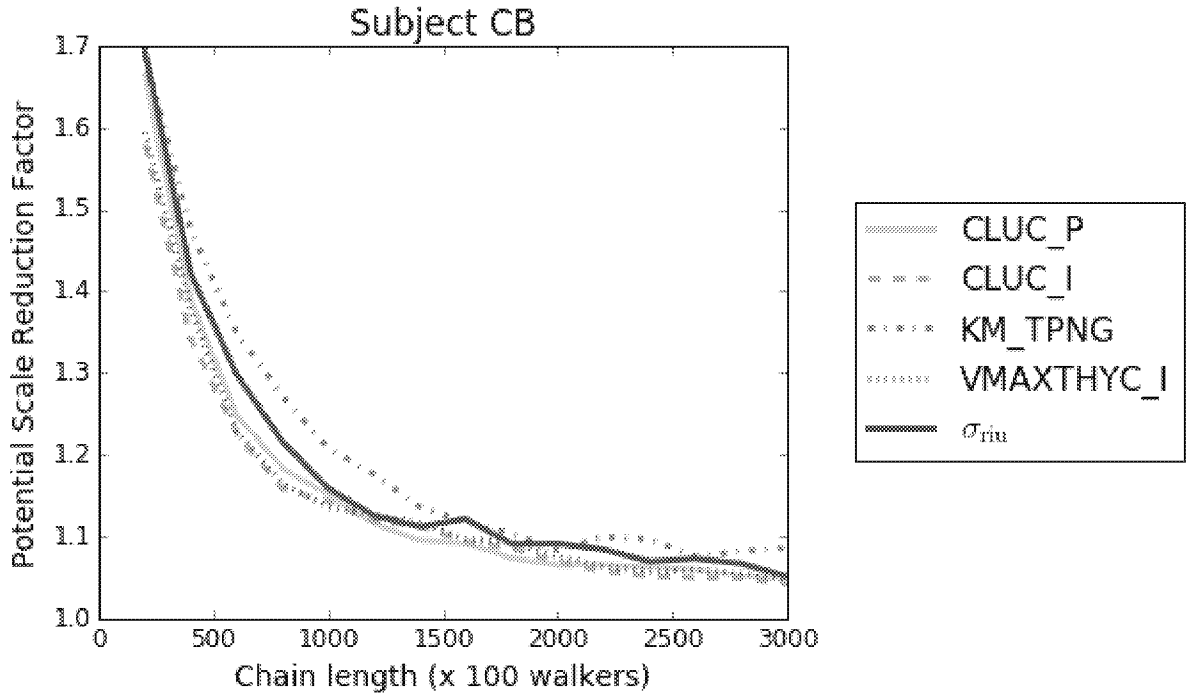
Figure A-6. Plot of the PSRF vs. the number of steps in each chain for subjects "CB" and "SV"



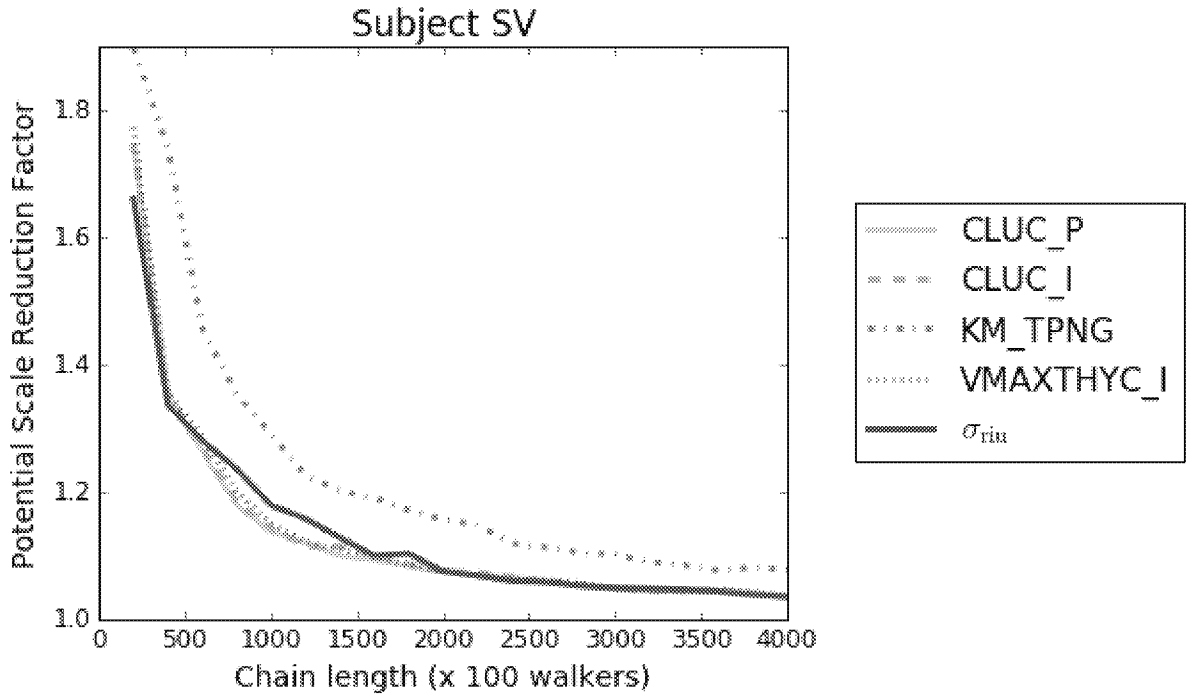


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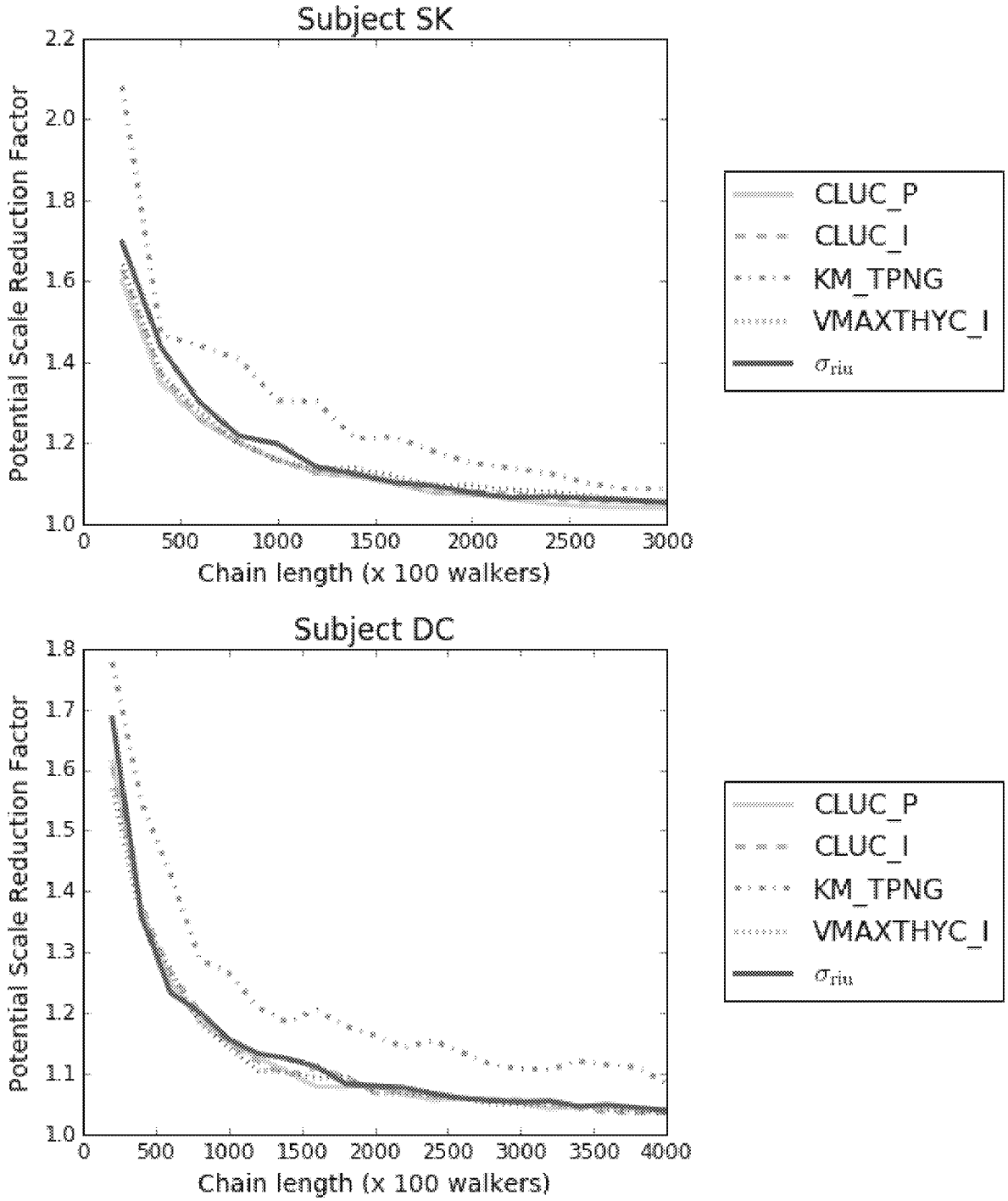
Figure A-7. Plot of the PSRF vs. the number of steps in each chain for subjects "SK" and "DC"



1.3.5 Parameter Estimation Results

For each of the 12 female subjects in the Greer et al. (2002) study, we obtained samples from the joint posterior distribution of the parameters. The results for one of the parameters (q_1 = CLUC_P) and one

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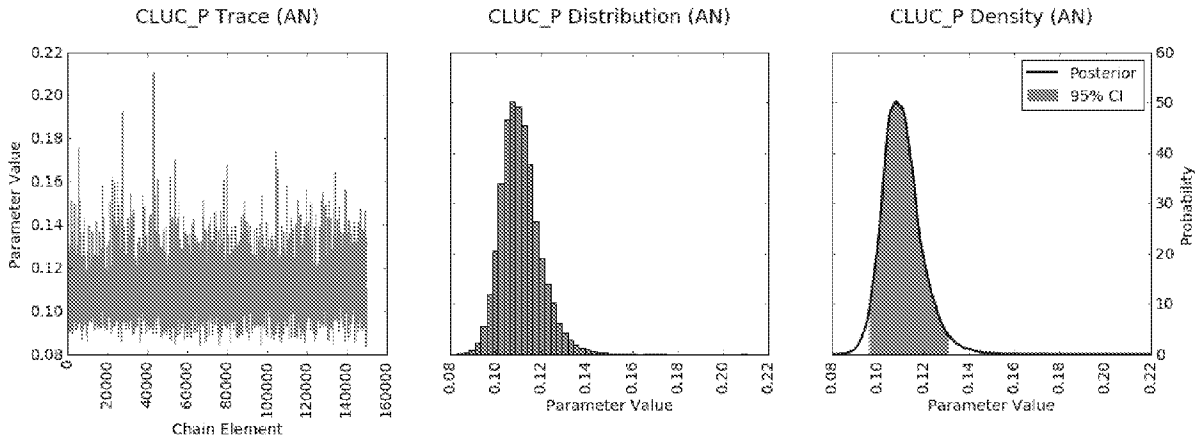
of the subjects ("AN") are illustrated in Figure A-8. Results for all four of the physiological parameters (q_1 = CLUC_P, q_2 = CLUC_I, q_3 = KM_TPNG, and q_4 = VMAXTHYC_I) for this same subject are illustrated in Figure A-9 , and results for all four of the biochemical parameters for the remaining subjects are illustrated in Figure A-10 through Figure A-20.

Figure A-8. MCMC Results for the parameter q_1 = CLUC_P using data from the Greer et al. (2002) study for subject "AN"[a]



[a] The left panel shows the value of this parameter for 150,000 (100 chains × 1500 steps) samples from the posterior distribution. The middle panel shows a relative frequency histogram generated from these 150,000 values. The right panel shows a smoothed representation of the distribution of values created using kernel density estimation. In the right panel, the shaded area under the curve indicates a 95% credible interval that is obtained by setting a lower limit at the 2.5th percentile of the sampled values and an upper limit at the 97.5th percentile of the sampled values.

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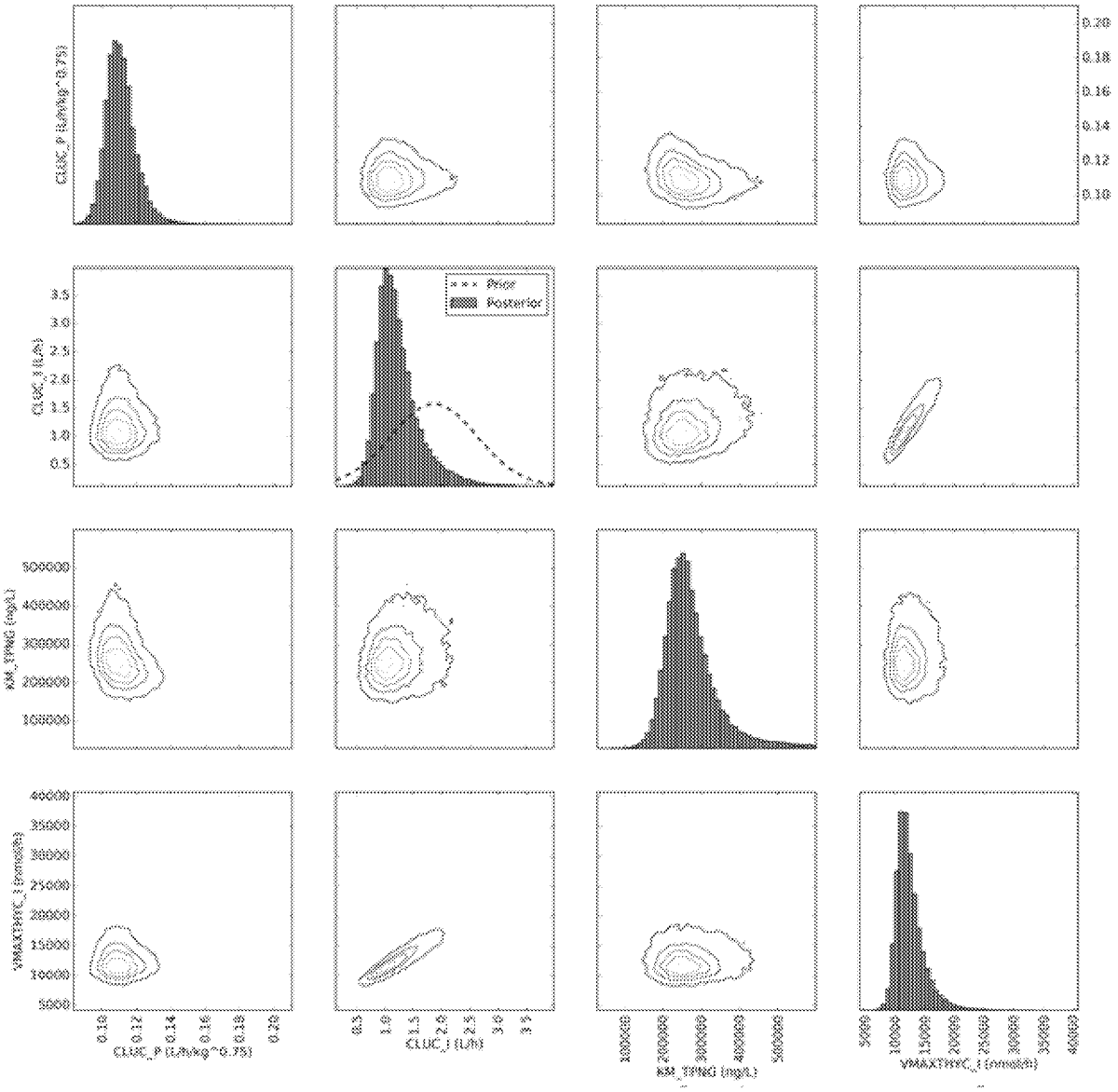
Figure A-9. Marginal and pairwise joint distributions of estimated parameters for subject "AN"[a]



[a] Marginal (panels on the diagonal) and pairwise joint (panels off the diagonal) distributions for CLUC_P, CLUC_I, KM_TPNG, and VMAXTHYC_I, using data from Greer et al. (2002). The marginal prior is shown for CLUC_I; for other parameters, the priors were flat. Outermost (purple) contours in the (off-diagonal) pairwise joint distribution plots indicate 90% credible regions for the parameters involved. Other contours indicate 70, 50, 30, and 10% (innermost, yellow) credible regions.

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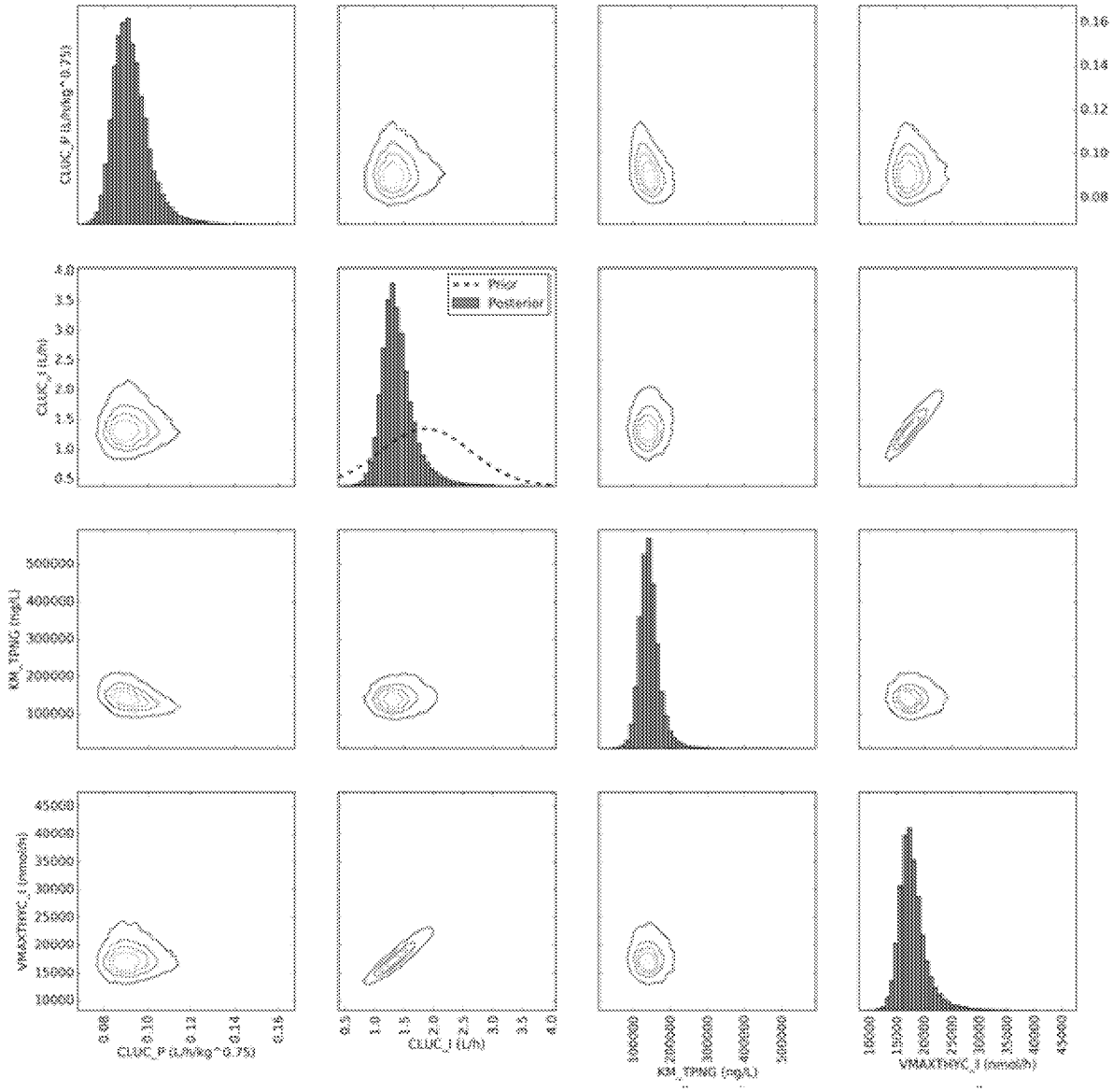
Figure A-10. Marginal and pairwise joint distributions of estimated parameters for subject "CW"[a]



[a] See Figure A-9 footnote.

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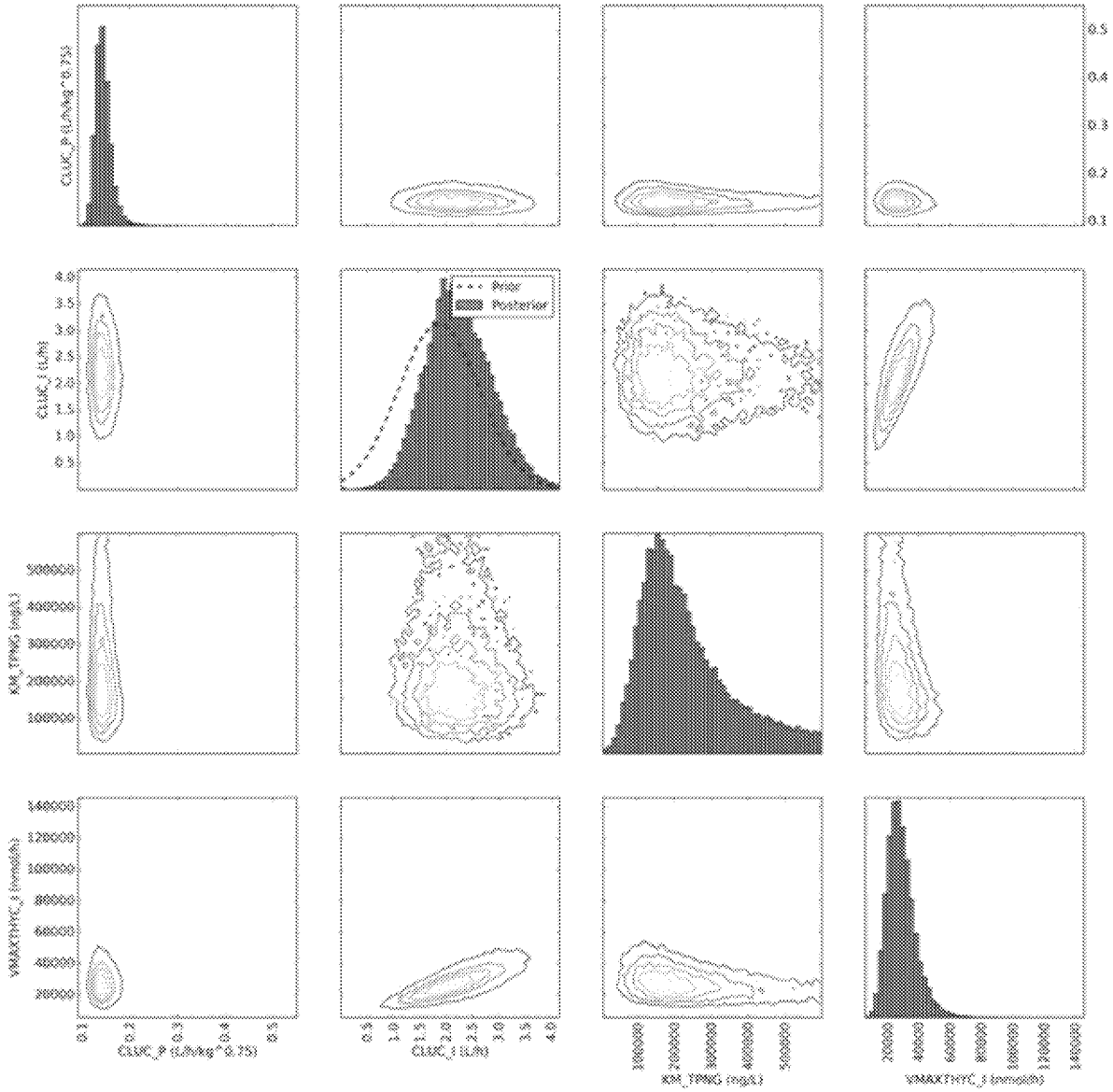
Figure A-11. Marginal and pairwise joint distributions of estimated parameters for subject "AB1"[a]



[a] See Figure A-9 footnote.

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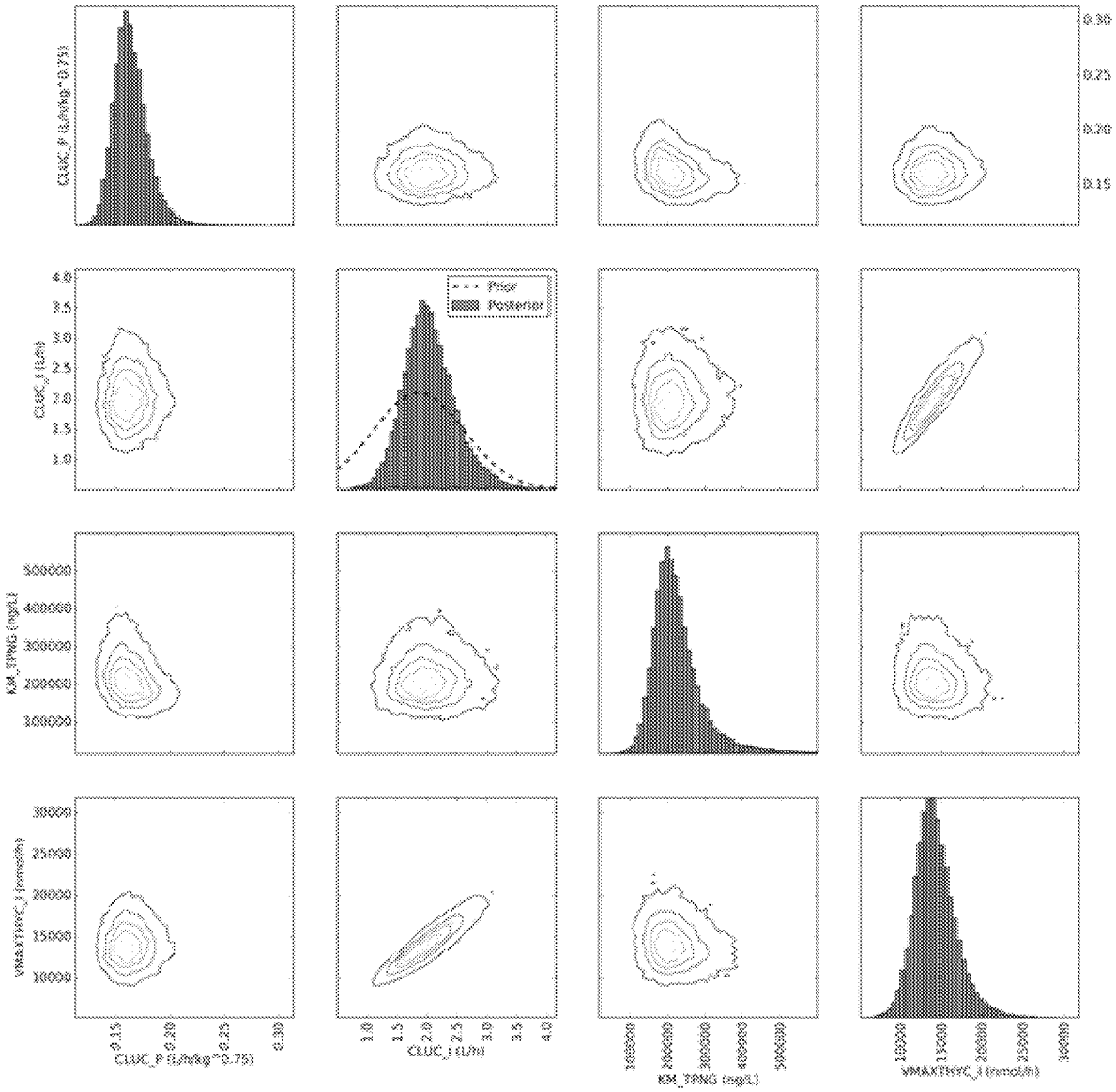
Figure A-12. Marginal and pairwise joint distributions of estimated parameters for subject "RC"[a]



[a] See Figure A-9 footnote.

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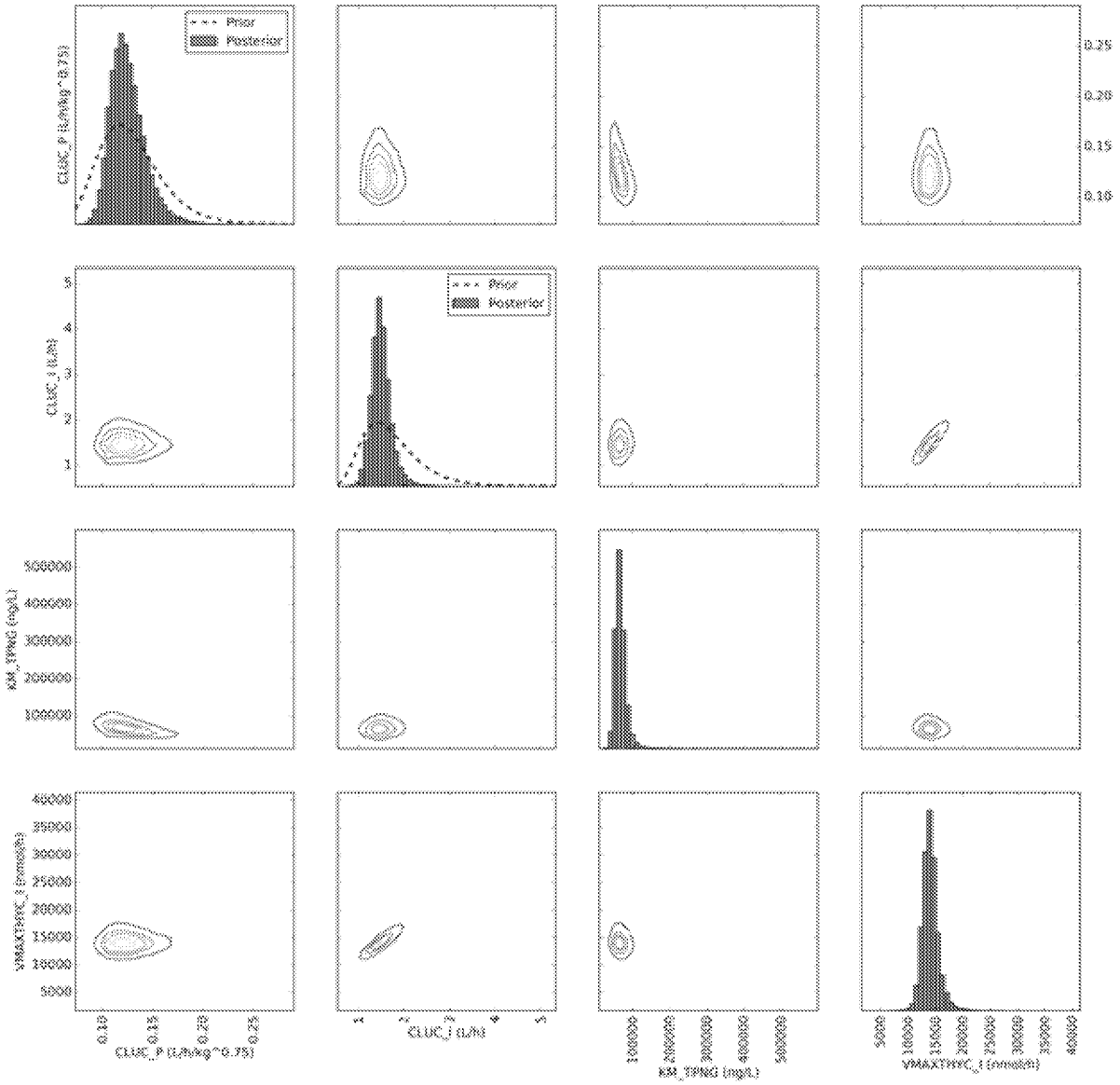
Figure A-13. Marginal and pairwise joint distributions of estimated parameters for subject "RT"[a]



[a] See Figure A-9 footnote.

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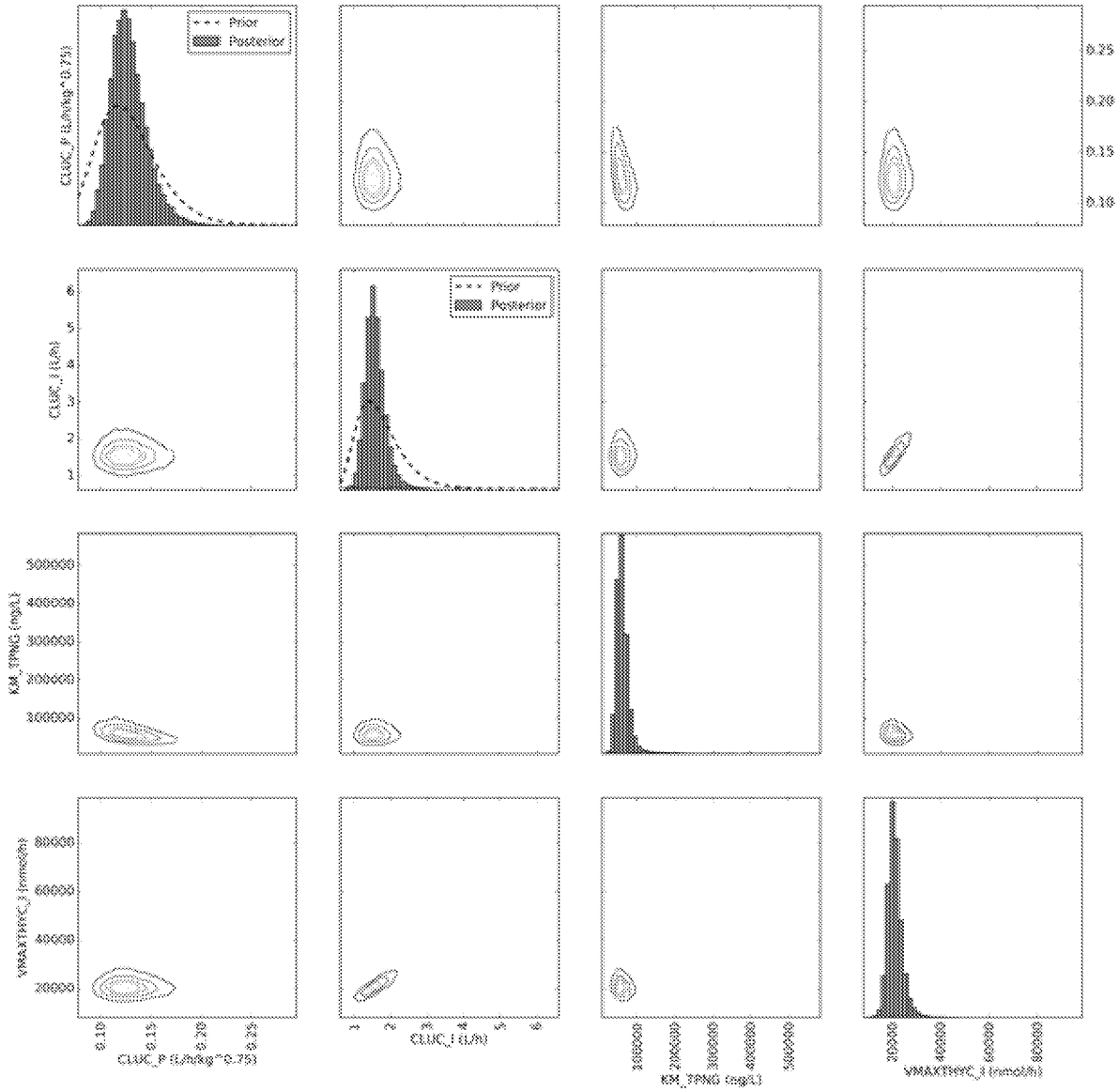
Figure A-14. Marginal and pairwise joint distributions of estimated parameters for subject "JF"[a]



[a] See Figure A-9 footnote.

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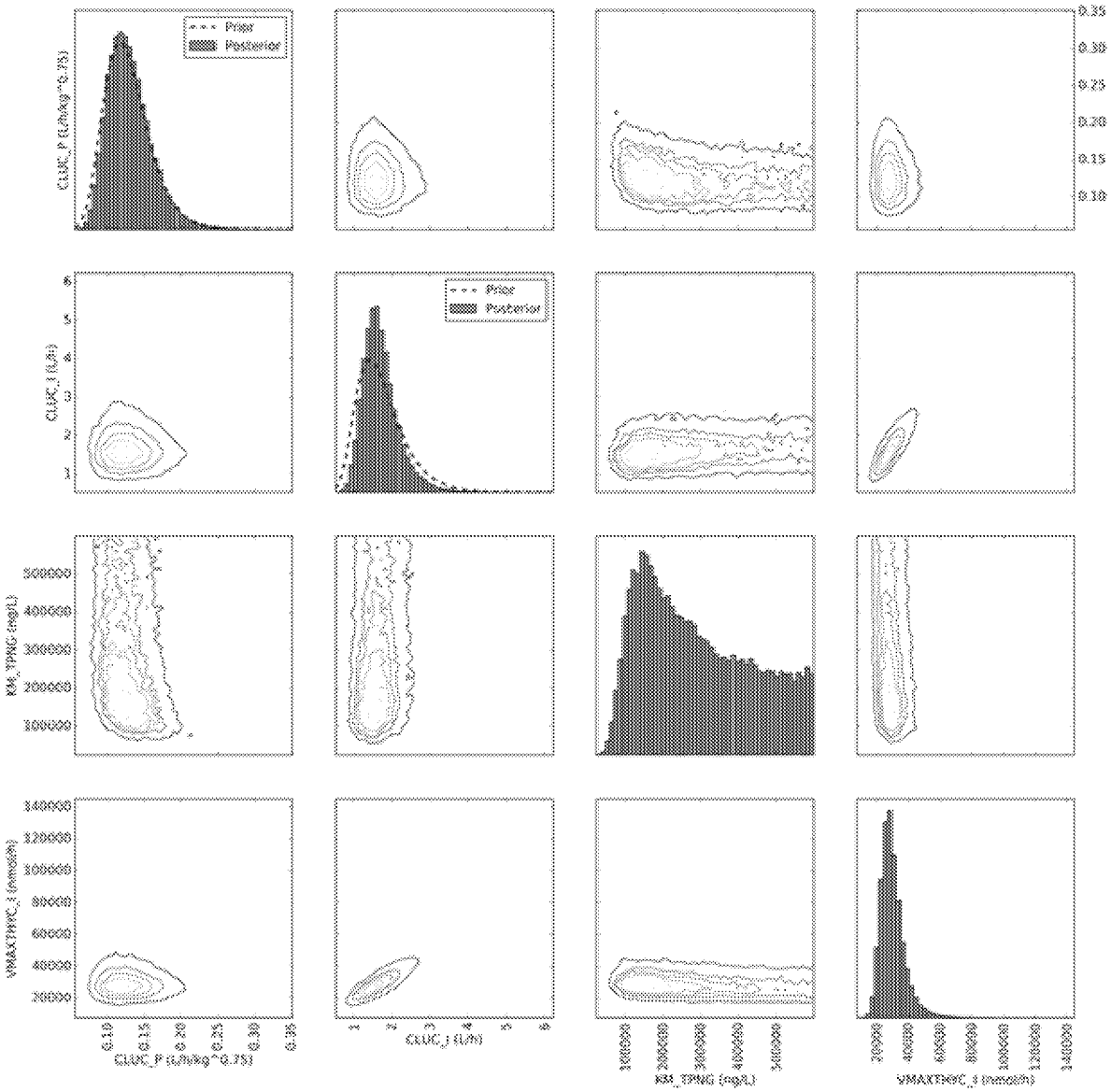
Figure A-15. Marginal and pairwise joint distributions of estimated parameters for subject "AH"[a]



[a] See Figure A-9 footnote.

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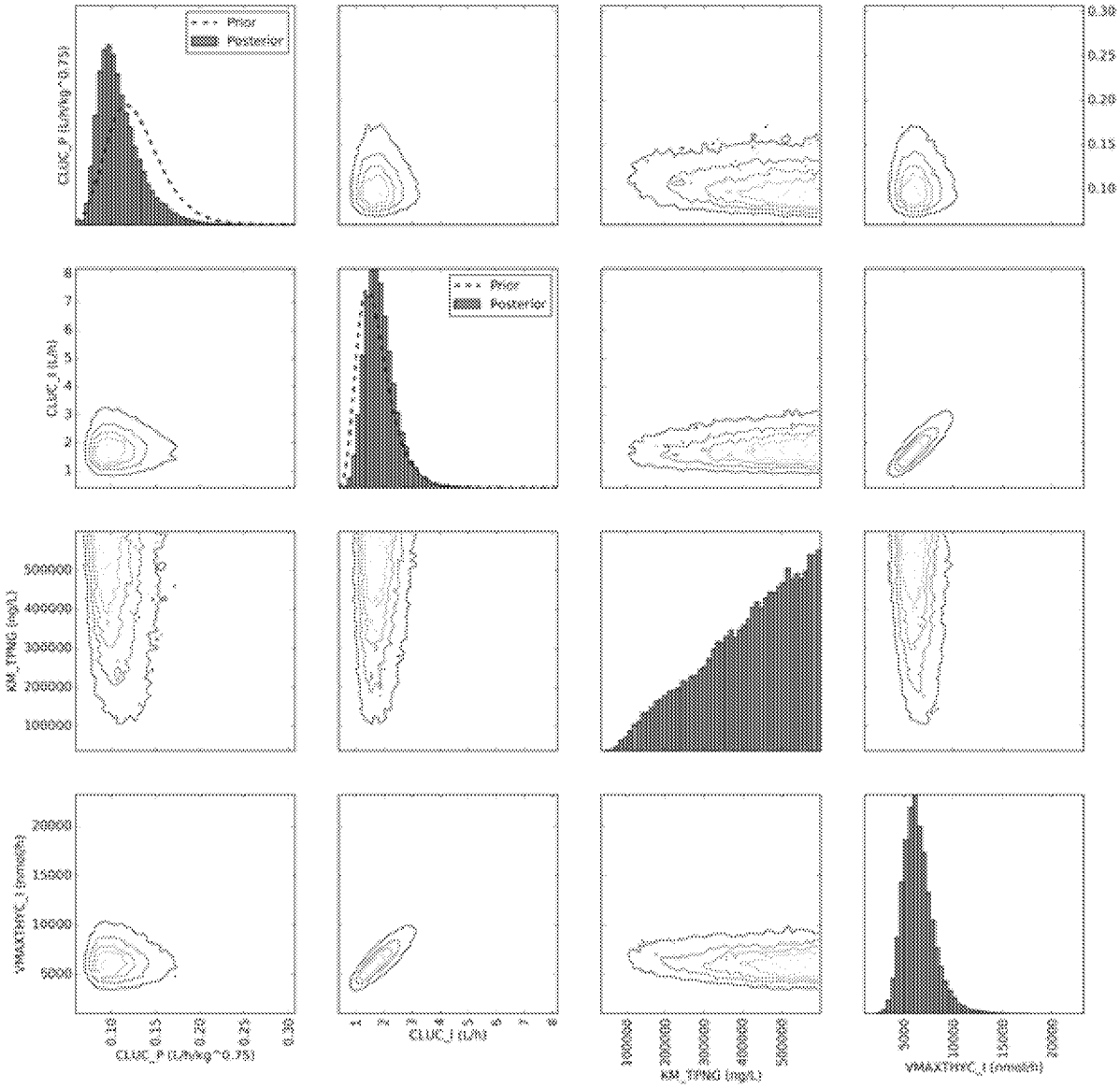
Figure A-16. Marginal and pairwise joint distributions of estimated parameters for subject "SG"[a]



[a] See Figure A-9 footnote.

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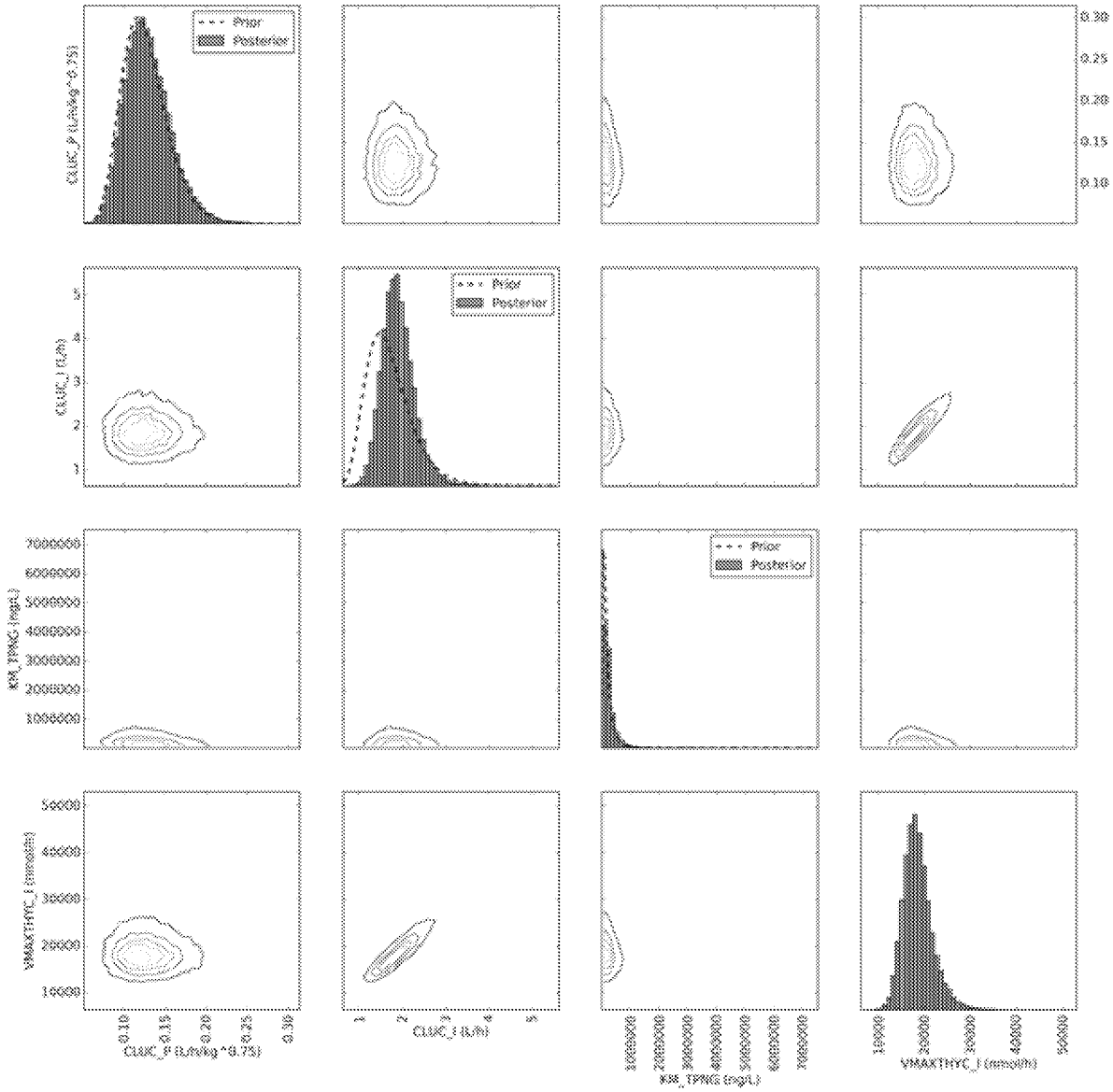
Figure A-17. Marginal and pairwise joint distributions of estimated parameters for subject "CB"[a]



[a] See Figure A-9 footnote.

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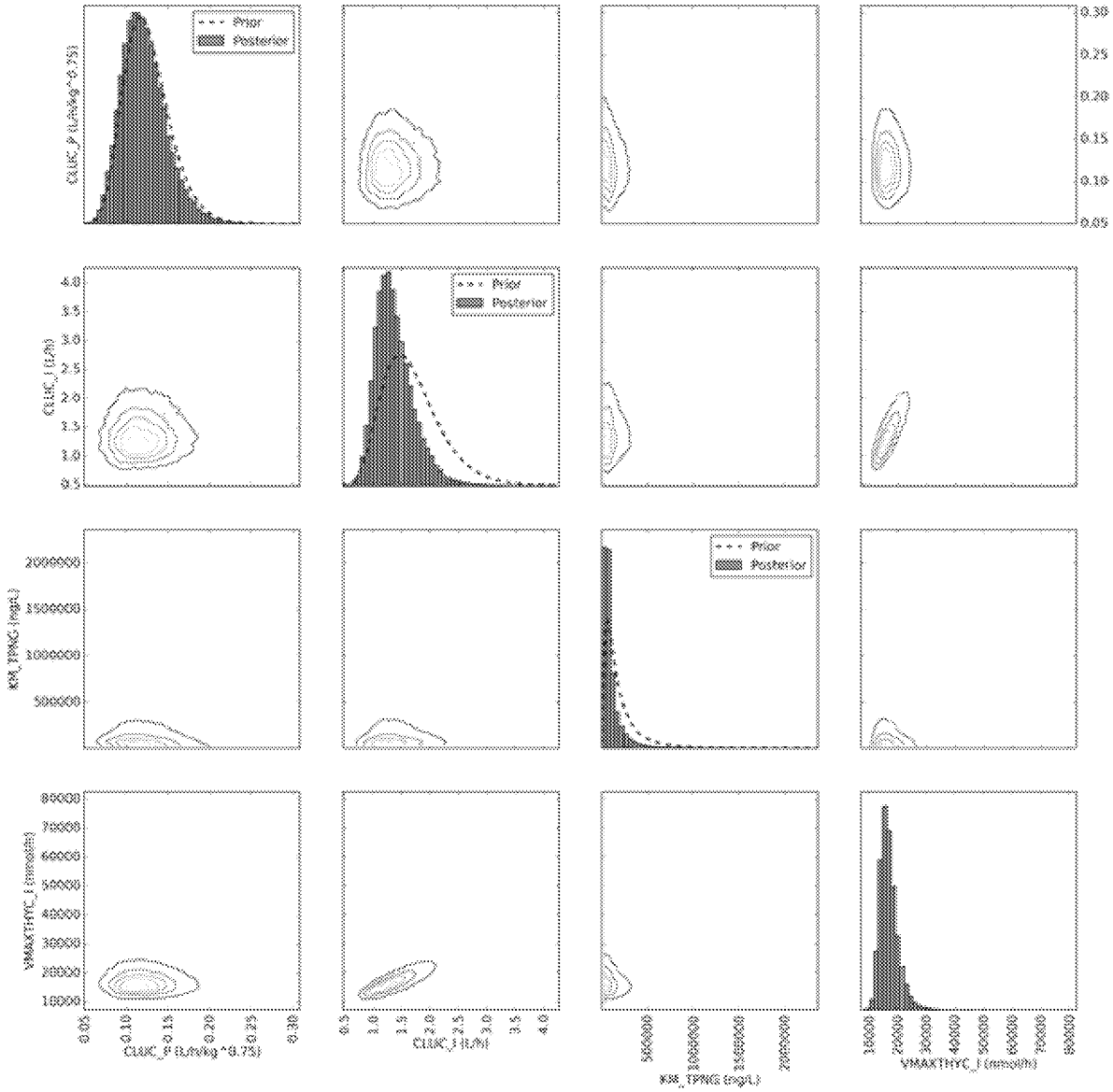
Figure A-18. Marginal and pairwise joint distributions of estimated parameters for subject "SV"[a]



[a] See Figure A-9 footnote.

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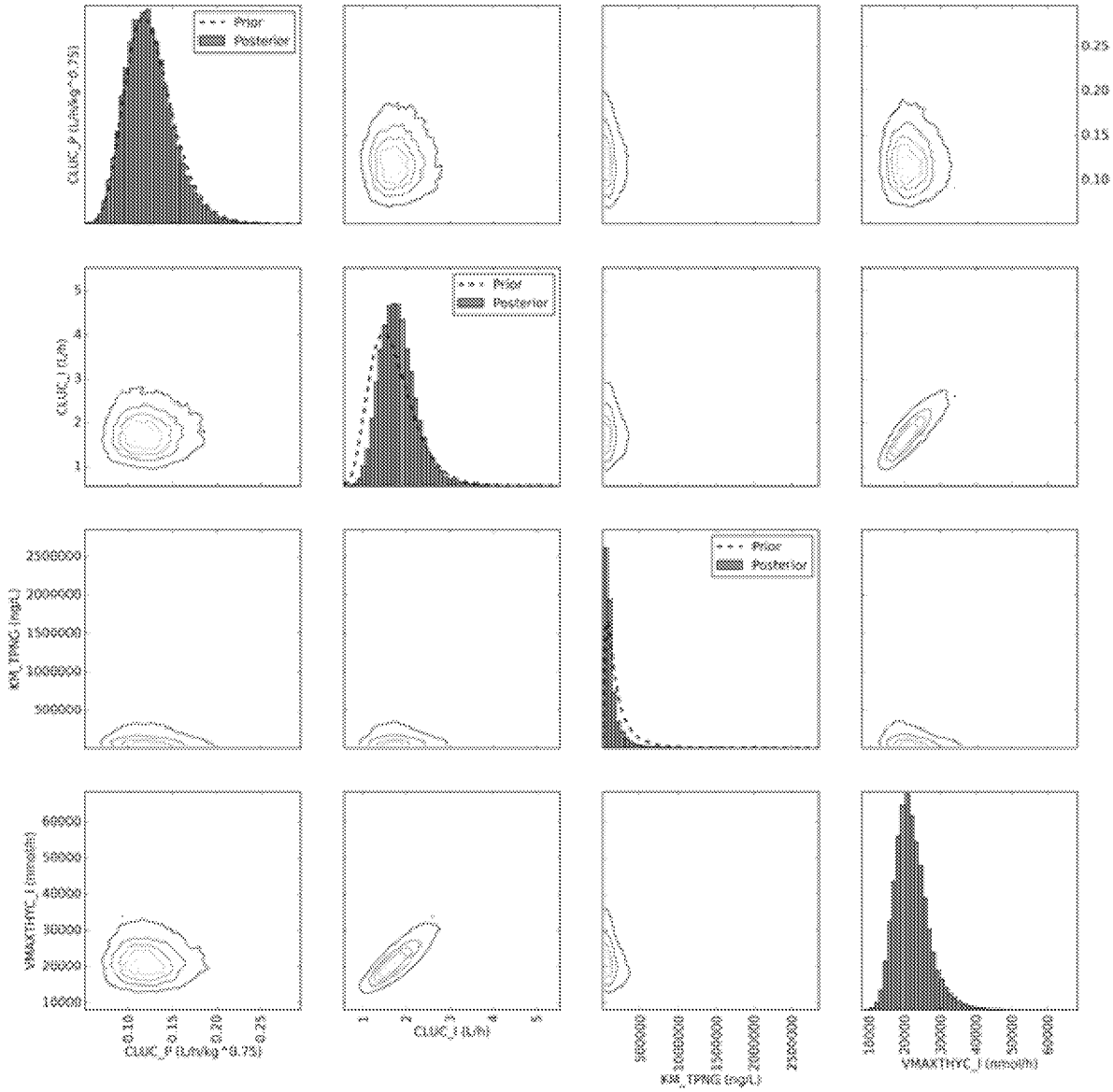
Figure A-19. Marginal and pairwise joint distributions of estimated parameters for subject "SK"[a]



[a] See Figure A-9 footnote.

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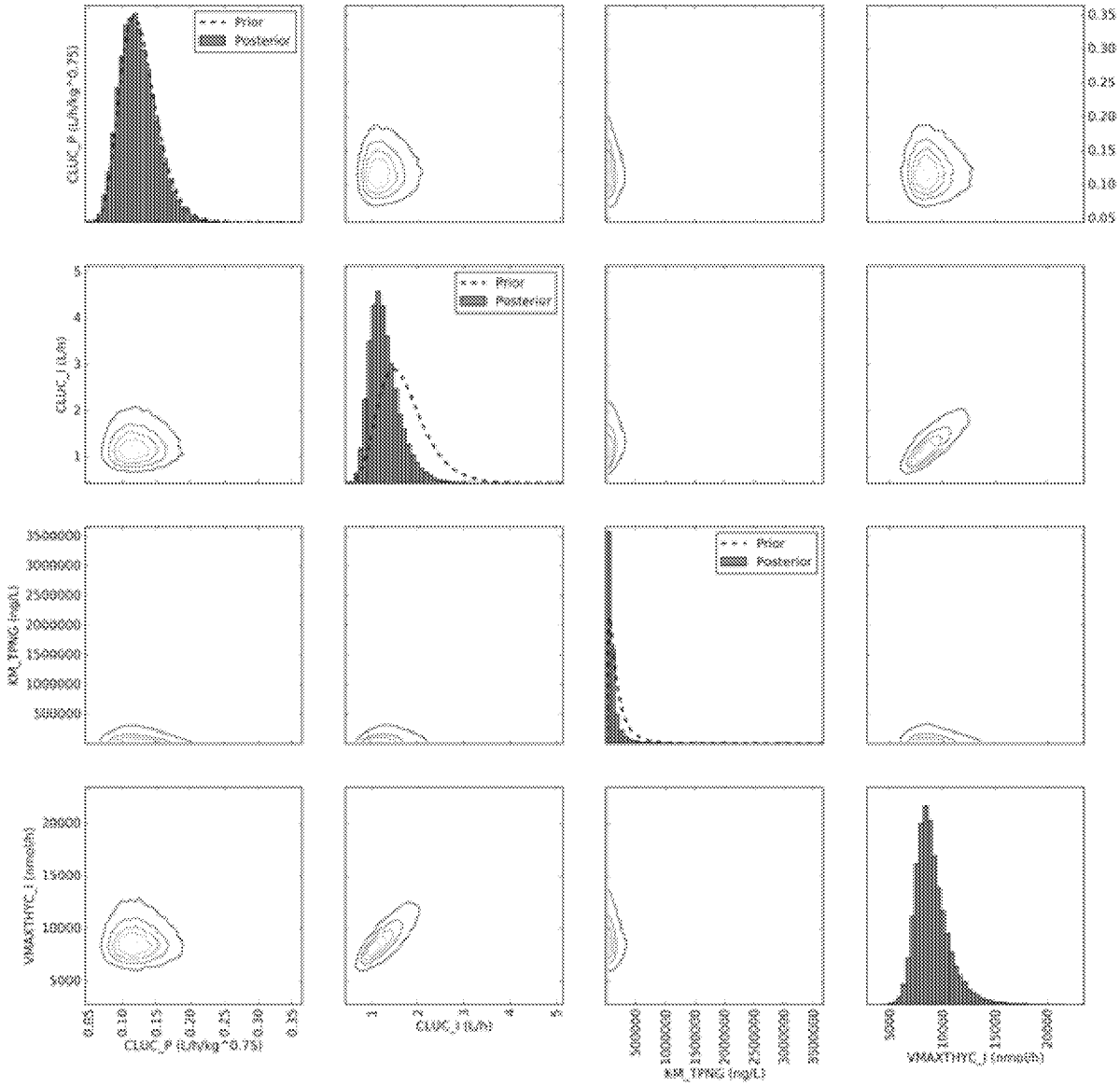
Figure A-20. Marginal and pairwise joint distributions of estimated parameters for subject "DC"[a]



[a] See Figure A-9 footnote.

With the exception of CLUC_I and VMAXTHYC_I, we found that the estimated parameters were independently distributed. For example, when examining the distribution of values along any vertical line through the contour plot in the first row and second column of Figure A-9 (representing the pairwise joint distribution of CLUC_P and CLUC_I, the resulting conditional distribution for CLUC_P would not be substantially different than one that arises for any other vertical line. For the pairwise joint distribution of CLUC_I and VMAXTHYC_I, this is clearly not the case – the two parameters have a significant linear correlation. This is an "identifiability" issue that arises because the data we are using do not contain sufficient information for us to uniquely identify both of the parameters in question: CLUC_I, the rate of urinary clearance of iodide, and VMAXTHYC_I, the maximum rate of uptake of iodide by the thyroid. That is, there are many pairings of CLUC_I and VMAXTHYC_I (taken from the linear trend line that defines the long axis of the ovals that can be

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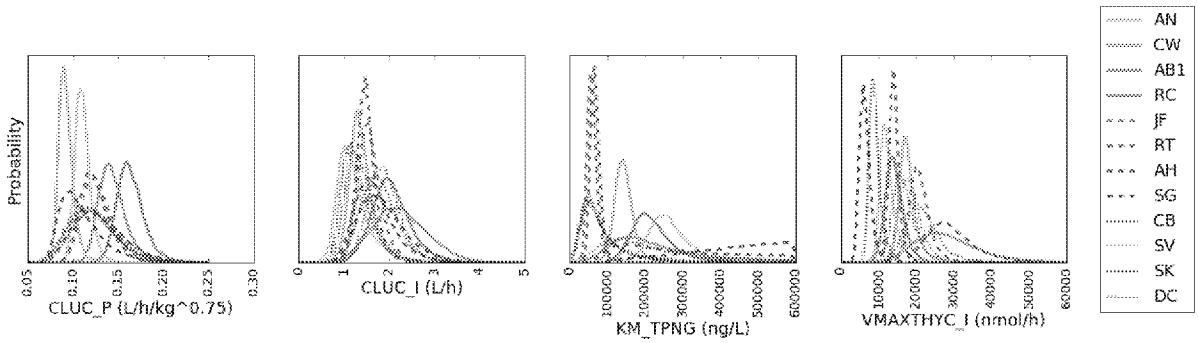
seen in the contour plot in the fourth row and second column of Figure A-9) for which the iodide uptake by the thyroid would be the same.

Marginal distributions for all four physiological parameters and all twelve female subjects are shown in Figure A-21. In this figure, solid lines, dashed lines, and dotted lines illustrate distributions for the subjects from the high-dose group (AN, CW, AB1, and RC), mid-dose group (JF, RT, AH, and SG), and low dose group (CB, SV, SK, and DC), respectively. Each individual curve gives a sense of the intra-individual (within subject) uncertainty for a given parameter, whereas comparing the different curves for that parameter gives a sense of the inter-individual (between subject) variability for the parameter.

Figure A-21. Individual marginal distributions for four physiological parameters[a]



[a] Distributions based upon individual posterior sample results for twelve female subjects from the study of Greer et al. (2002).

Values of the parameter KM_TPNG tend to be larger for subjects in the high-dose group than for subjects in the mid- and low-dose groups (i.e., the distributions for mid- and low-dose subjects tend to be "stochastically greater" than those for high-dose subjects). From a chemical and biological standpoint, it is not likely that this parameter, which describes a binding affinity of perchlorate for the sodium iodide symporter (NIS), would be influenced by dose. It is considered more likely that the higher values of KM_TPNG observed for subjects in the high-dose group reflect a deficiency in the parameter estimation scheme and/or the underlying BBDR model used for this calibration. In particular, the non-lactating mother BBDR model does not account for the possibility of an up-regulation of NIS levels over time, but rather assumes that there is a constant maximum rate of iodide uptake by the thyroid (VMAXTHYC_I). If the model allowed for VMAXTHYC_I to vary in time (e.g., in response to elevated perchlorate exposure and decreased thyroid hormone production) it is conceivable that data for the high-dose subjects would be consistent with a lower value of the parameter KM_TPNG. We chose to use a constant value for VMAXTHYC_I, as allowing this parameter to vary in time would result in parameter identifiability issues and would not further inform the BBDR model with respect to our ultimate purpose: predicting responses to lower (environmentally relevant) perchlorate exposures.

Figure A-22 shows the distributions for the population median values of four biochemical parameters that are obtained when sampling from the posterior sample results for all twelve female subjects. Assuming the 12 subjects are representative of the human female population in the US, these distributions illustrate the uncertainty in the population-level median for each parameter (where the population is adult women in the US). Some descriptive statistics for these sampling distributions of the medians are provided in Table A-5.

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Figure A-22. Sampling distributions of the medians for four estimated parameters based upon posterior sample results for twelve female subjects from the study of (Greer, et al., 2002)

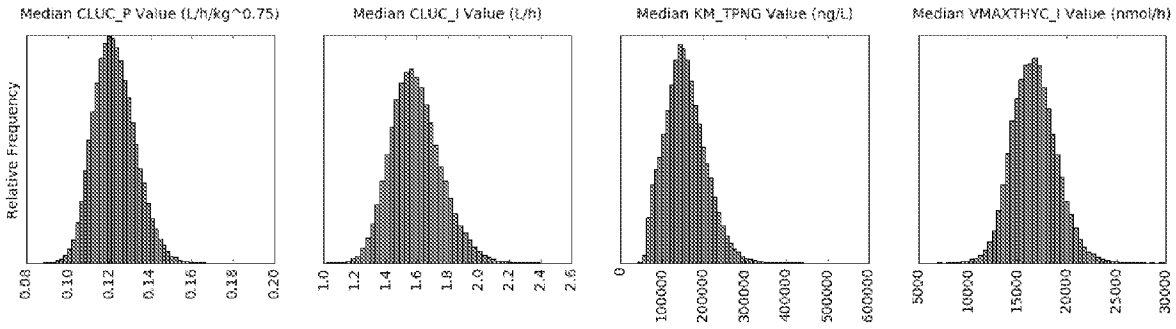

Table A-5. Descriptive statistics for the sampling distribution of the median values for CLUC_P, CLUC_I, KM_TPNG, and VMAXTHYC_I.[a]

Parameter	Units	Mean	Standard Deviation	50th Percentile	2.5th Percentile	97.5th Percentile
CLUC_P (CLFUP)	$L/h/kg^{0.75}$	0.123	0.00996	0.122	0.105	0.143
CLUC_I (CLFUI)	L/h ($L/h/kg^{0.75}$)	1.59 (0.0657)	0.162 (0.00669)	1.58 (0.0653)	1.31 (0.0541)	1.94 (0.0802)
KM_TPNG (KMNIS_P)	ng/L (nM)	1.55×10^5 (1560)	4.90×10^4 (493)	1.51×10^5 (1520)	7.16×10^4 (720)	2.60×10^5 (2610)
VMAXTHYC_I (VMAXNIS_THY_I)	nmol/h ($nmol/h/kg^{0.75}$)	1.67×10^4 (690)	2.26×10^3 (93.4)	1.66×10^4 (686)	1.26×10^4 (521)	2.14×10^4 (884)

[a] Primary parameter names, units, and values are those for the adapted lactation PBPK model (U.S. EPA, 2016) used for this analysis. Names, units, and values in parentheses are for the corresponding parameters in the 1T BBDR model, as listed in Table A-2.

As was already described, distributional estimates of KM_TPNG tend toward much higher values for the high-dose subjects. This is also true for two of the mid-dose subjects. We therefore considered two alternative methods for obtaining the sampling distribution of the median for KM_TPNG. In the first alternative approach (A1), we used the same bootstrapping method previously described to select a group of subjects, but in this case we only selected 8 subjects (with replacement) from the 8 mid- and low-dose subjects. In the second alternative approach (A2), we used the same method, but we only selected 6 subjects (with replacement) from the 6 subjects for whom the distributional estimates for KM_TPNG seemed reasonable: JF, RT, CB, SV, SK, and DC. The sampling distributions for the median of KM_TPNG that arise from these alternatives are compared with the distribution we obtained using the originally proposed method (using distributions for all 12 subjects) in Figure A-23. Some descriptive statistics for the sampling distributions of the median of KM_TPNG obtained by these different methods are provided in Table A-6.

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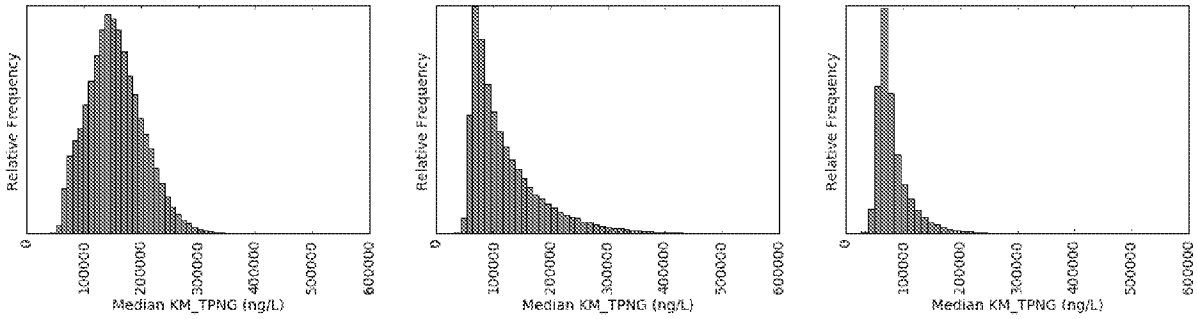
Figure A-23. Comparison of alternate sampling distributions for the median of KM_TPNG[a]



(a) **(b)** **(c)**

[a] Sampling distributions of KM_TPNG using (a) the original method (with all 12 subjects), (b) method A1 (with 8 subjects) and (c) method A2 (with 6 subjects).

Table A-6. Descriptive statistics for the sampling distribution of the median of KM_TPNG (ng/L) (KMNIS_P (nM)) obtained using three different approaches.

Method	Number of Subjects	Mean	Standard Deviation	50th Percentile	2.5th Percentile	97.5th Percentile
Original	12	1.55×10^5 (1560)	4.90×10^4 (493)	1.51×10^5 (1520)	7.16×10^4 (720)	2.60×10^5 (2610)
A1	8	1.22×10^5 (1230)	6.60×10^4 (664)	1.00×10^5 (1010)	5.62×10^4 (565)	3.03×10^5 (3050)
A2	6	8.28×10^4 (833)	3.31×10^4 (333)	7.28×10^4 (732)	4.86×10^4 (489)	1.74×10^5 (1750)

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1.4 Gestation-Specific Physiological Parameters

1.4.1 Body Weight (BW)

BW increase in early pregnancy is relatively modest and does not have a large effect on model predictions. Therefore, recent review document on pregnancy physiology (Abduljalil, Furness, Johnson, Rostami-Hodjegan, & Soltani, 2012) and two previous reviews (ICRP-89, 2002; NAS, 1990) were considered sufficient as sources of data on gestational weight gain and were considered to be sufficient for establishing a central tendency in the population. For the more recent review by Abduljalil et al. (2012), the data were evaluated for accuracy and information on the subject population and method for determining gestational weight gain in as many of original references cited in the review articles as could be obtained. References were not obtained for data from ICRP-89 (2002) and NAS (1990), because 1) the references primarily had data for gestation after week 16, and 2) the majority of the sources were from the 1930s to 1970s and not readily available through electronic resources.

For original data sources, the information was entered into a spreadsheets using the publication's original units and converted to gestational weight gain in kg. For references listing body weight during pregnancy, the weight gain was calculated based on the pre-pregnancy body weight listed in the reference. The weight gain reported in Cheikh Ismail et al. (2016) was calculated based on the weight measured at the first obstetric visit during the 1st trimester, and therefore may be a low estimate of the weight gain during gestation. Other factors that contribute to variability in recorded weight gain include the source of the pre-pregnancy weight (e.g., subject recall or actual clinical measure) and the accuracy of the date of gestation age (i.e., based on recall of date of last menstrual period or verified by ultrasound by developmental markers).

Figure A-24 shows gestation weight gain data from a number of sources for gestation age up to 20 weeks. For the time-points, the specific week was used for references listing exact gestational age at the time of measurement. For references reporting data by trimesters, the convention used from literature was 1st trimester as weeks 1 to 12, 2nd trimester as weeks 13 to 27, and 3rd trimester as weeks 28 to birth. For the 2nd and 3rd trimesters, the median weeks of 20 and 34 were used. For the 1st trimester 9 weeks was used as the median between 6 and 12 weeks to represent the likely window of time for the 1st obstetric visit after conception.

The Gompertz growth curve generally has the form:

$$\mathrm{BW(t)} = W_0 \cdot exp\left\{\frac{r_0}{\alpha}\left[1 - e^{-\alpha \cdot t}\right]\right\}$$

To obtain a model of mass gain for a typical mother, we utilized data depicted by Hytten & Leitch (1971), who reported the mean mass gain during pregnancy of 2868 "normotensive primigravidae" (i.e., women who were pregnant for the first time and who maintained blood pressure in the normal range). The actual data are not provided by Hytten and Leitch (1971), so the data were extracted from the coordinates of points from their mass gain trend curve. Least squares regression was used to fit the Gompertz growth model for these points, to obtain: $W_0 = 0.0065$ kg, $r_0 = 0.68$/week, and $\alpha = 0.087$/week.

However, we seek a model that connects seamlessly with the non-pregnant BW, BW_0, assumed to be constant for an indefinite time preceding gestation. Therefore, the equation for growth was added to

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BW_0, but with a slight correction for the Gompertz growth value at gestation week zero (GW = 0 weeks):

$$\mathrm{BW(GW)} = BW_0 + 0.0065 \cdot \left(exp\left\{\frac{0.68}{0.87}[1 - e^{-0.87 \cdot GW}]\right\} - 1\right)$$

Use of the equation as indicted implicitly assumes that variation in BW at any given gestational age is due to variation in the initial/non-pregnant body weight, BW_0. While literature has shown a correlation of weight gain during pregnancy with the body mass index (BMI) (NAS, 1990), the rate of gain as a function of pre-pregnancy body weight has not been established. In addition, there are other biological factors besides the pre-pregnancy body weight that affect the variability of weight gain among pregnant women, including maternal age, ethnicity, socioeconomic status, and number of previous pregnancies. Given that variation in initial thyroid kinetic parameters is explicitly included in the model, and perchlorate dosing is described per kg BW, failure to incorporate this additional level of variation in BW during the 1st trimester is not expected to add significantly to the uncertainty in BBDR model predictions.

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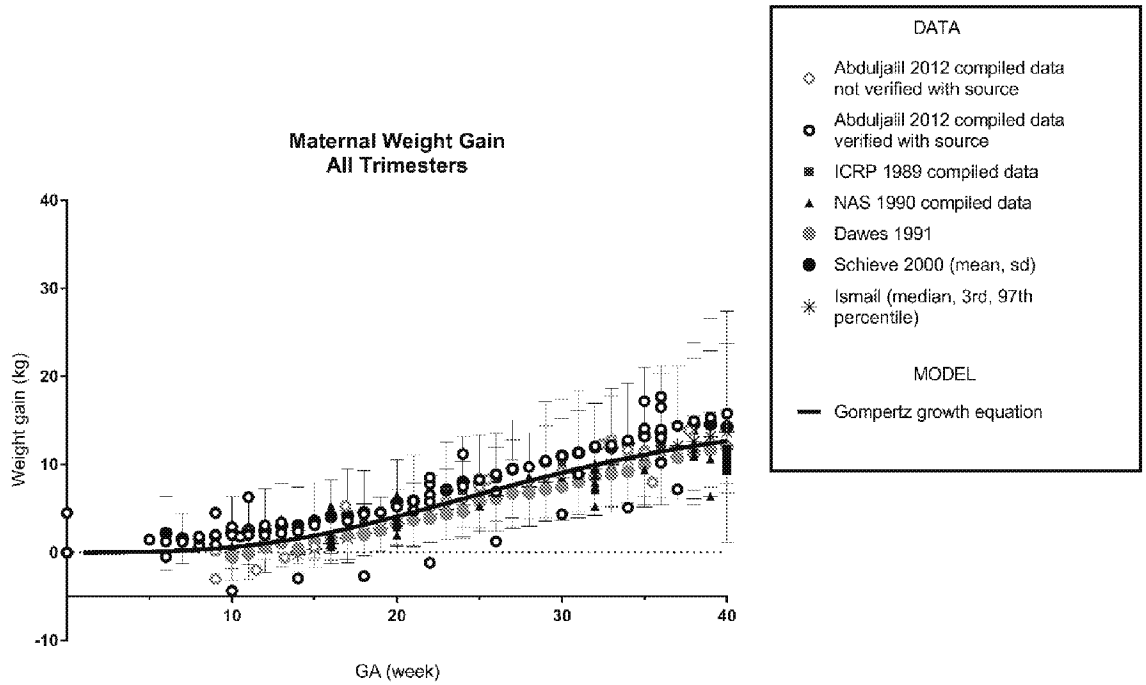
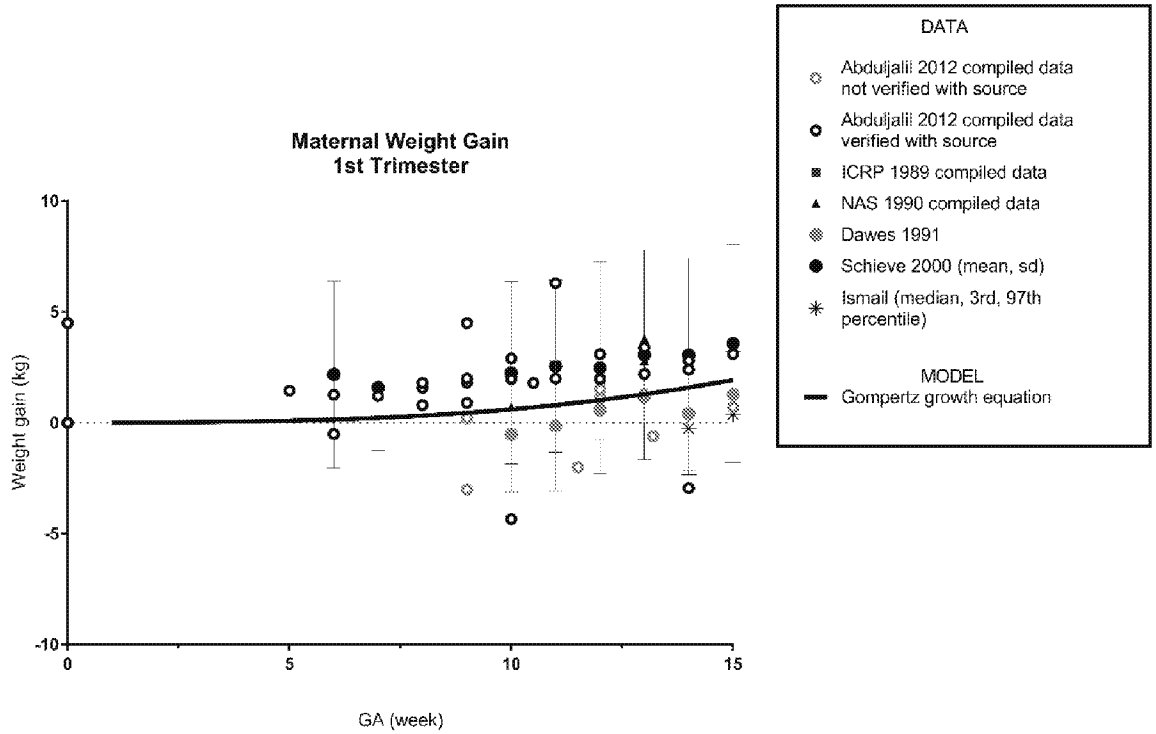
Figure A-24. Maternal Weight Change During Pregnancy[a]





[a] Data for weight change during pregnancy vs. before pregnancy from various populations (Abduljalil, et al., 2012; Butte, Ellis, Wong, Hopkinson, & Smith, 2003; Chapman et al., 1998; Cheikh Ismail, et al., 2016; ICRP-89, 2002; Larciprete et al., 2003; Lof et al., 2005; NAS, 1990; Schieve et al., 2000).

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1.4.2 Cardiac Output

Like BW, cardiac output (total blood flow) only has a modest impact on model predictions. The recent review from Abduljalil et al (2012) contained a compilation of values over pregnancy which were therefore considered sufficient for use in setting a central tendency during the 1st trimester. The data were evaluated for accuracy and information on the subject population and method for determining cardiac output in as many of original references cited in the review articles as could be obtained. Data could be verified for all but one of the ten cited sources. An additional reference (Mabie, DiSessa, Crocker, Sibai, & Arheart, 1994) was identified during the literature search for thyroid volume data.

While Gaohua, Abduljalil, Jamei, Johnson, & Rostami-Hodjegan, (2012) has previously published a 2nd order polynomial equation to predict the increase in cardiac output during pregnancy, their algorithm appeared to under-predict the increase in cardiac output in the 1st trimester. Therefore, the compiled data were analyzed with Prism version 7 software (GraphPad Software Inc.) to determine the empirical model with the best fit to the data over the course of pregnancy. For references that gave measures of cardiac output that were measured during a range of gestation ages, the median of the range was used for the time point of the data. The data were analyzed accounting for the standard deviations and number of subject among the various literature studies. The preferred fit from Prism was an exponential equation (details in Table A-1):

$$QC(GW) = 293.8 + 140.7 \cdot (1 - exp^{-0.1027 \cdot GW})$$

Figure A-25 shows the exponential equation fit with the literature data for cardiac output during all trimesters of pregnancy.

If the initial cardiac output, QC_0 (293.8 L/h for these data) is assumed to vary with initial maternal BW, but the factor for increase in QC (QC_G = 141.4 L/h) is assumed to be independent of QC_0, then the equation can be written as:

$$QC(GW) = QC_0 + QC_G \cdot (1 - e^{-0.1027 \cdot GW})$$

Since the BBDR model assumes QC varies as $BW^{0.75}$ using a multiplicative constant, the cardiac index (QFC), the value of QFC for non-pregnant women, QFC_0, is calculated using the value of QC_0 from this regression and the pre-pregnancy BW from Chapman et al. (1998) (61.5 kg). This data set was used since the mean cardiac output for that group closely matches the exponential regression equation and they reported BW values allowing calculation of QFC. The resulting value of QFC_0 is 13.378 L/(h-$kg^{0.75}$). The final form of the equation is:

$$QC(GW) = QFC_0 \cdot BW_0^{0.75} + QC_G \cdot (1 - e^{-0.1009 \cdot GW}).$$

To characterize the variation in QC increase during pregnancy, independent of QC_0, one would need individual subject data on QC before pregnancy and during pregnancy. These data are not available and model predictions are not expected to be highly sensitive to QC. Therefore, only variation in QC due to the dependent variation in BW_0 is incorporated.

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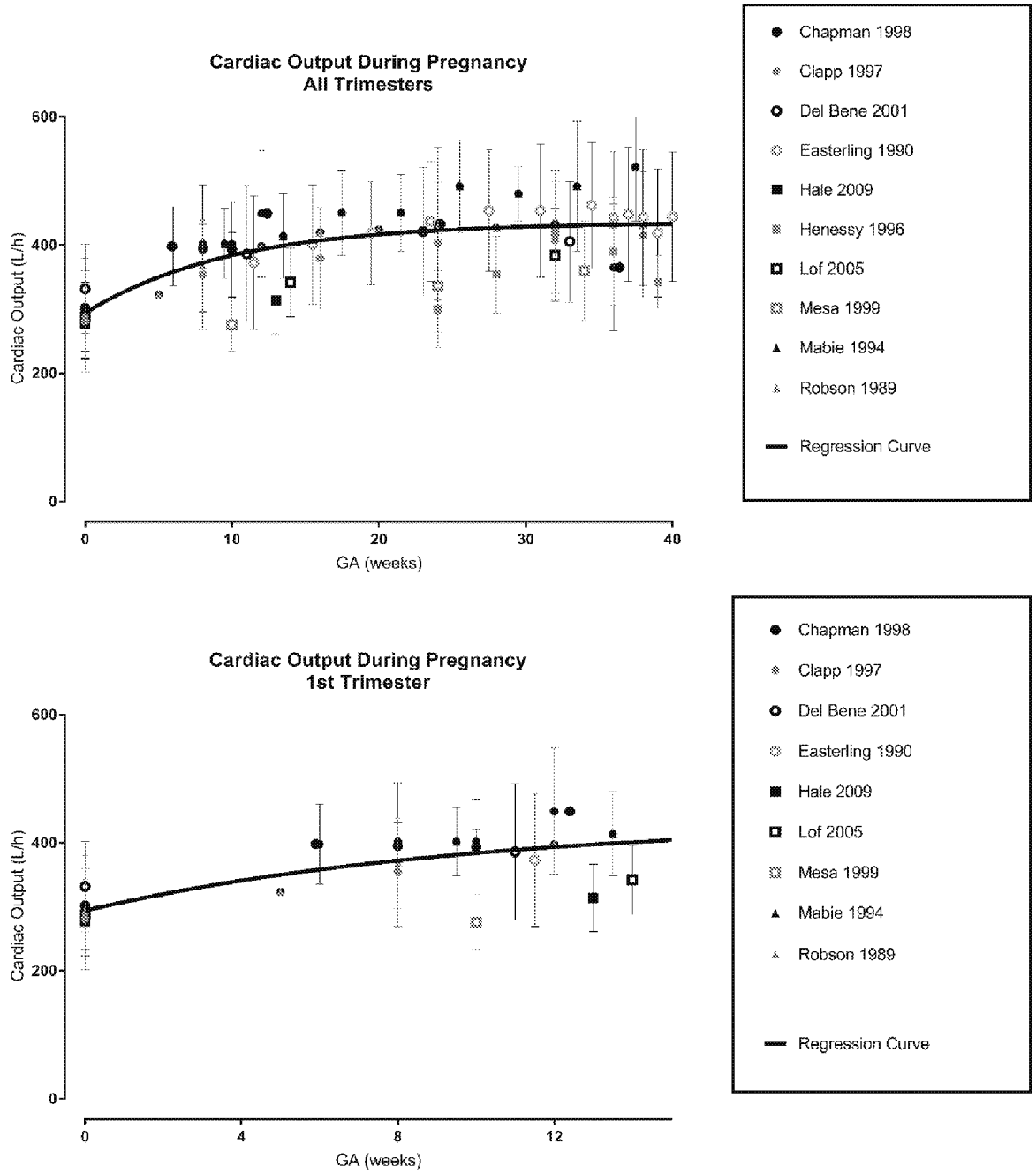
Figure A-25. Change in total cardiac output with gestation age[a]



[a] Data for total cardiac output during pregnancy from multiple populations (Chapman, et al., 1998; Clapp & Capeless, 1997; Del Bene et al., 2001; Easterling, Benedetti, Schmucker, & Millard, 1990; Hale, Schonberg, Badger, & Bernstein, 2009; Hennessy et al., 1996; Lof, et al., 2005; Mabie, et al., 1994; Mesa et al., 1999; Robson, Dunlop, Boys, & Hunter, 1989) are shown vs. a regression curve, described in the text.

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1.4.3 Plasma Volume

Data compiled by Abduljalil, et al. (2012) for plasma volume values over pregnancy were considered sufficient for use in setting a central tendency during the 1st trimester. The data were evaluated for accuracy and information on the subject population and method for determining plasma volume in as many of original references cited in the review articles that could be obtained. Because many of the references were from 1950s to 1970s, only 6 of the 16 sources cited could be verified against original references.

While Gaohua et al. (2012) has previously published a 3rd order polynomial equation to predict the change in plasma volume during pregnancy, their algorithm coefficients result in a predicted reduction in the plasma volume during the first few weeks of gestation, which is not clearly supported by the data in the first trimester. Therefore, the compiled data were analyzed with Prism version 7 software (GraphPad Software Inc.) to determine the empirical model with the best fit to the data over the course of pregnancy. For references that listed a gestation age range for the measured plasma volume, the median of the range was used for the time point of the data. The data were analyzed accounting for the standard deviations and n among the various literature studies. Based on the nonlinear regression analysis, a cubic model best fit the literature data (Table A-2):

$$Vpls(GW) = 2.512 + 0.004366 \cdot GW + 0.001751 \cdot GW^2 - 2.234e^{-5} \cdot GW^3$$

In order to use the equation expressed as a function of an initial plasma volume, which is calculated from a plasma volume fraction (Vfpls) and initial body weight (BW_0), the fitted equation was reduced to:

$$Vpls(GW) = Vpls_0 \cdot (1 + 0.001738 \cdot GW + 6.971 \times 10^{-4} \cdot GW^2 - 8.893 \times 10^{-6} \cdot GW^3)$$

The default Vfpls is set to 0.0359, which equals the fitted initial plasma volume of 2.512 L divided by BW_0 of 70 kg. Figure A-26 shows the literature values for plasma volume during pregnancy versus this regression curve.

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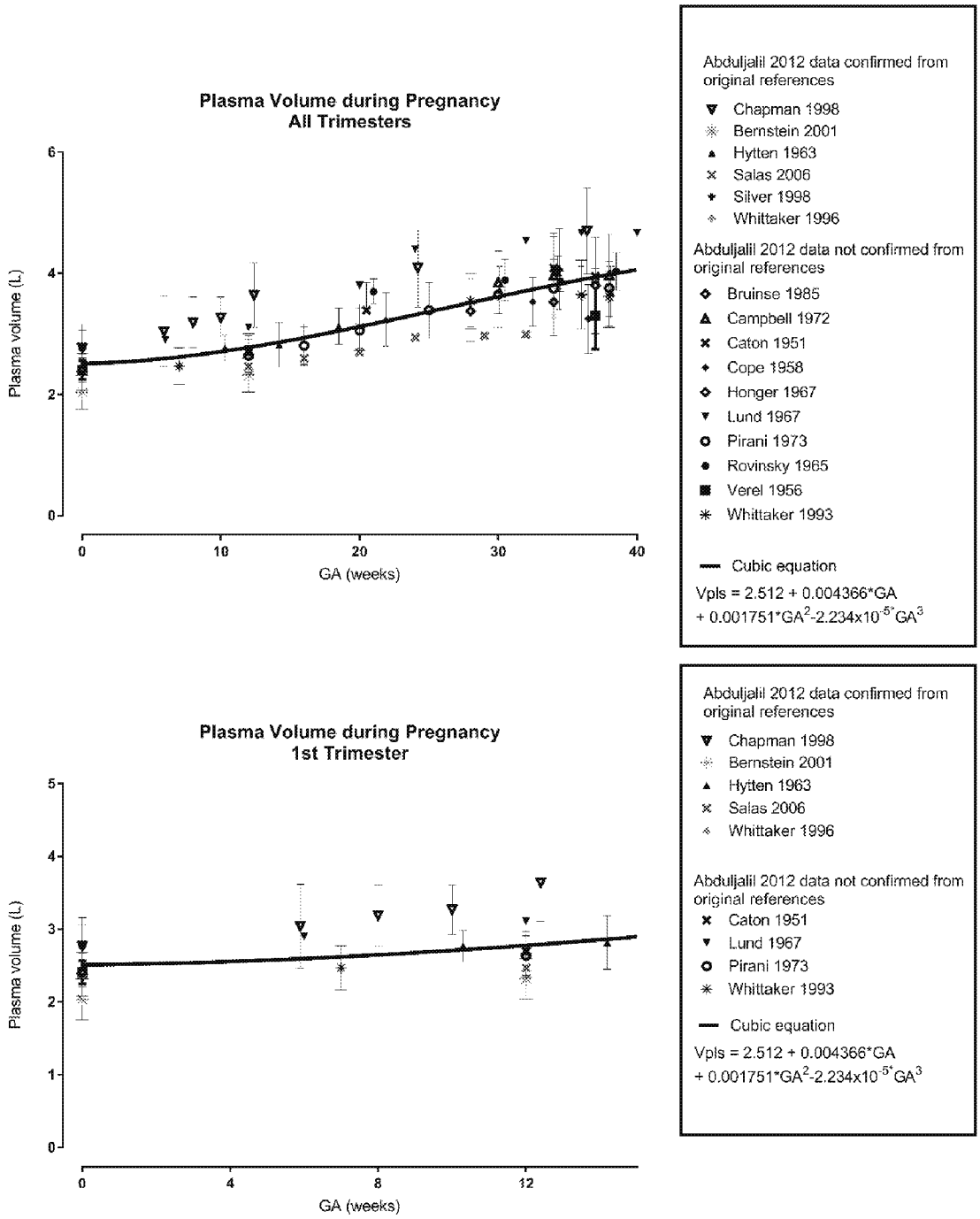
Figure A-26. Plasma Volume Changes[a]



[a] Data for plasma volume during pregnancy (Bernstein, Ziegler, & Badger, 2001; Bruinse, van den Berg, & Haspels, 1985; Campbell & MacGillivray, 1972; Caton et al., 1951; Chapman, et al., 1998; Cope, 1958; Honger, 1967; Hytten & Paintin, 1963; Lund & Donovan, 1967; Pirani, Campbell, & MacGillivray, 1973; Rovinsky & Jaffin, 1965; Salas, Marshall, Gutiérrez, & Rosso, 2006; Silver, Seebeck, & Carlson, 1998; Verel, Bury, & Hope, 1956; Whittaker & Lind, 1993; Whittaker, MacPhail, & Lind, 1996) are shown vs. a cubic equation weighted by the SD and N of each data set (see text for details).

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1.4.4 Hematocrit Percentage

Data compiled by Abduljalil et al. (2012) were considered sufficient for use in setting a central tendency during the 1st trimester. The data were evaluated for accuracy and information on the subject population and method for determining hematocrit amount in as many of original references cited in the review articles that could be obtained. Seven of the 12 references listed in Abduljalil et al. (2012) were able to be verified against the original references.

To be consistent with the analysis of the plasma volume, the compiled data were analyzed with Prism version 7 software (GraphPad Software Inc.) determine the empirical model with the best fit to the data over the course of pregnancy. For references that listed a gestation age range for the measured hematocrit, the median of the range was used for the time point of the data. The data were analyzed accounting for the standard deviations and n among the various literature studies. Based on the nonlinear regression analysis, a cubic model best fit the data (Table A-3):

$$Hct(GW)(\%) = 39.4 - 0.04117 \cdot GW - 0.00898 \cdot GW^2 + 0.0001763 \cdot GW^3$$

Since the model parameter of interest is actually red blood cell volume (VRbc), the following is used in the model to calculate VRbc from plasma volume (Vpls) and the percentage hematocrit in blood (Hct):

$$VRbc(GW) = \frac{Vpls(GW) \cdot Hct(GW)}{100 - Hct(GW)}$$

Figure A-27 shows the data values compared with the cubic equation over the course of pregnancy.

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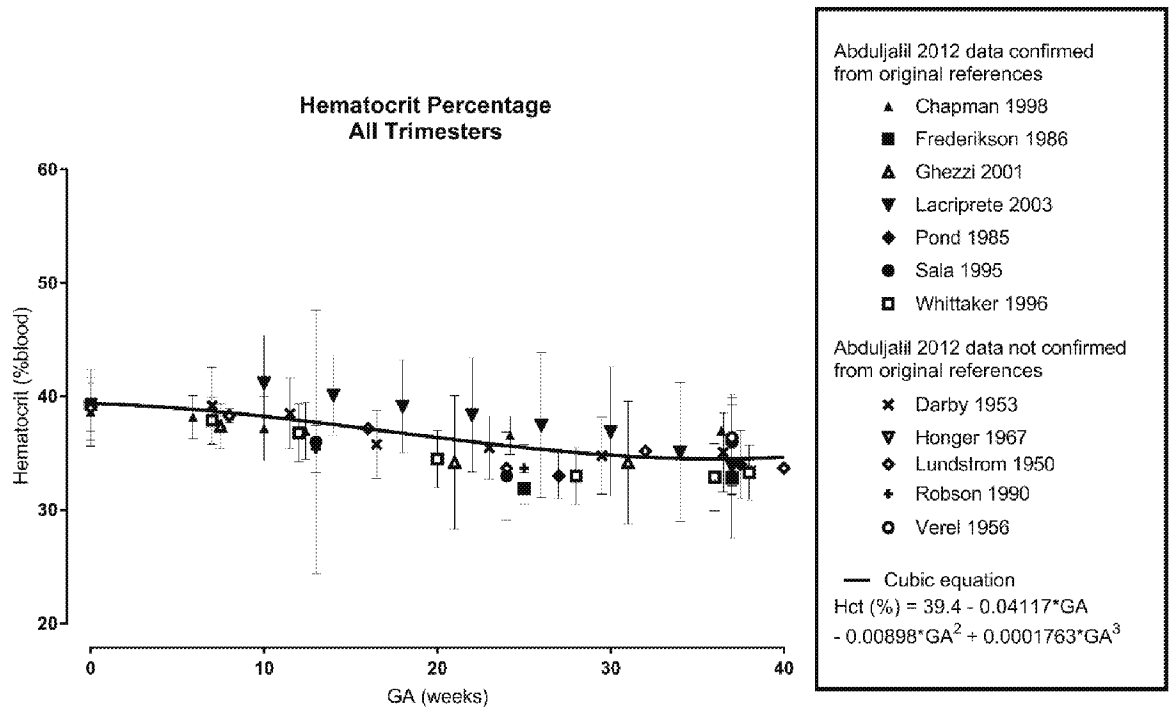
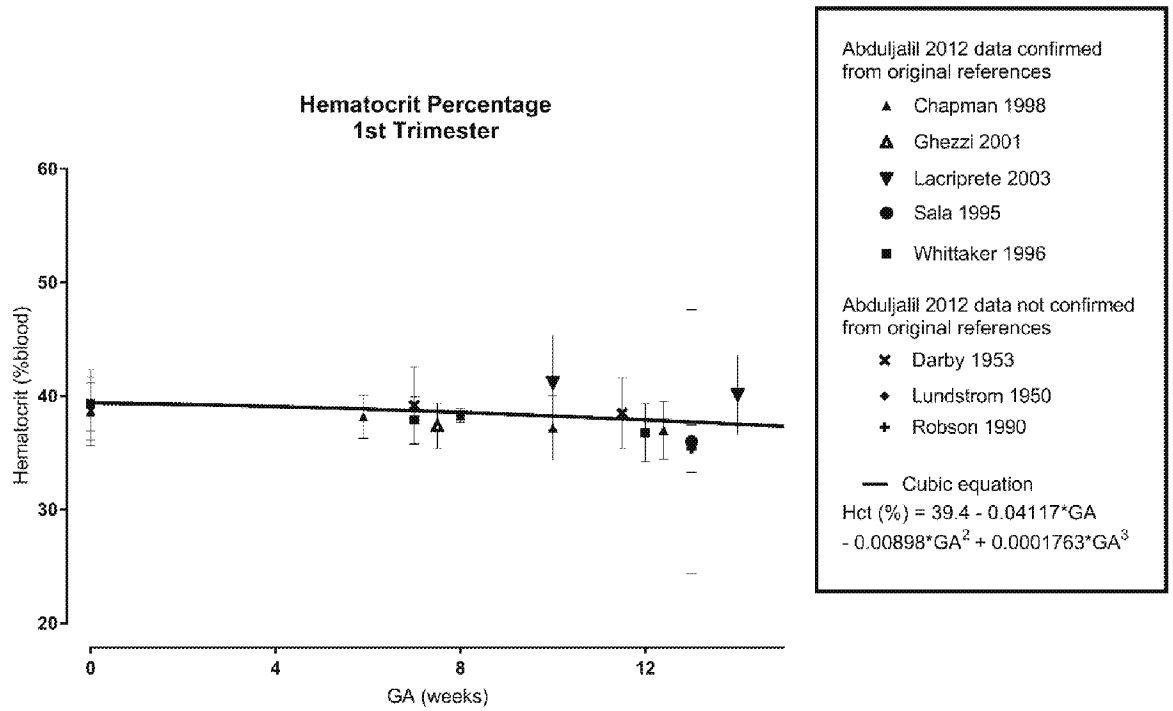
Figure A-27. Hematocrit (% of blood volume taken by red blood cells) during pregnancy[a]





[a] Data for hematocrit fraction during pregnancy (Chapman, et al., 1998; Darby et al., 1953; Frederiksen, Ruo, Chow, & Atkinson, 1986; Ghezzi et al., 2001; Honger, 1967; Larciprete, et al., 2003; Lundstrom, 1950; Pond, Kreek, Tong, Raghunath, & Benowitz, 1985; Robson, Mutch, Boys, & Woodhouse, 1990; Sala et al., 1995; Verel, et al., 1956; Whittaker, et al., 1996) are shown vs. a cubic equation weighted by the SD and N of each data set.

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1.4.5 Thyroid volume and blood flow

Abduljalil et al. (2012) did not include literature data for the thyroid volume during pregnancy. Therefore, a literature search was conducted on PubMed to identify references. Figure A-28 shows the search process that was used to search and filter potential references for review. The literature was not exhaustive, but was considered sufficient for identifying changes in the thyroid gland volume during the 1st trimester.

Figure A-29 shows the thyroid volume versus gestation age. Because the plot includes results from 25 different sources, the individual points are not identified for each study in the legend. The majority of the studies reported data based on trimesters; the data were entered for plotting and analysis according to the gestation age convention used for the previous physiological parameters, unless a specific gestation age during the trimester was given. One difference noted among the various studies is the inclusion of the isthmus in the determination of the total volume of the thyroid. Some references specifically stated whether the isthmus was included in the ultrasound can and calculation of total thyroid volume, while the information was not specified in the majority of the references. All references were combined for the purpose of plotting and analysis.

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Figure A-28. Search strategy for data on thyroid volume changes during pregnancy

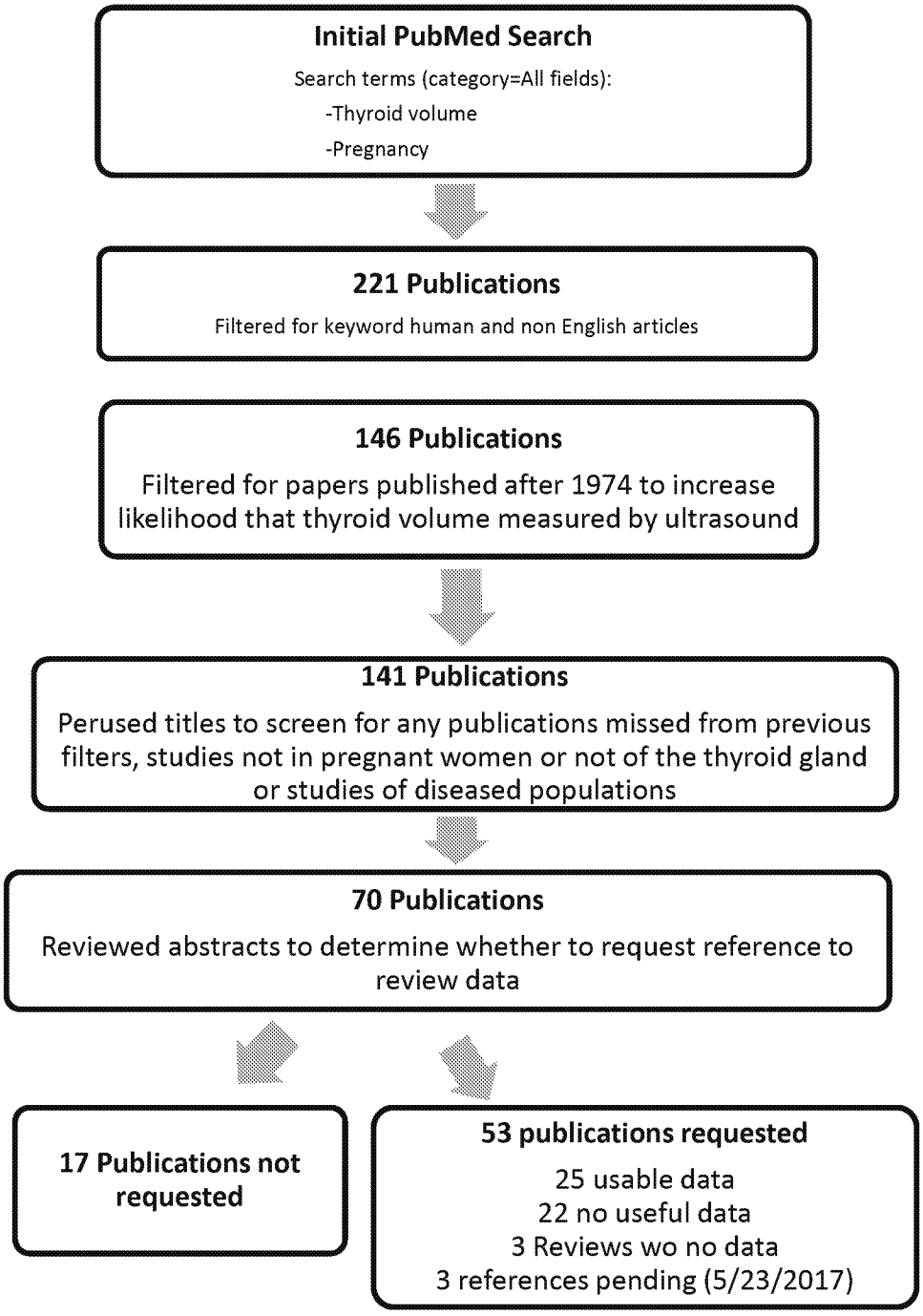

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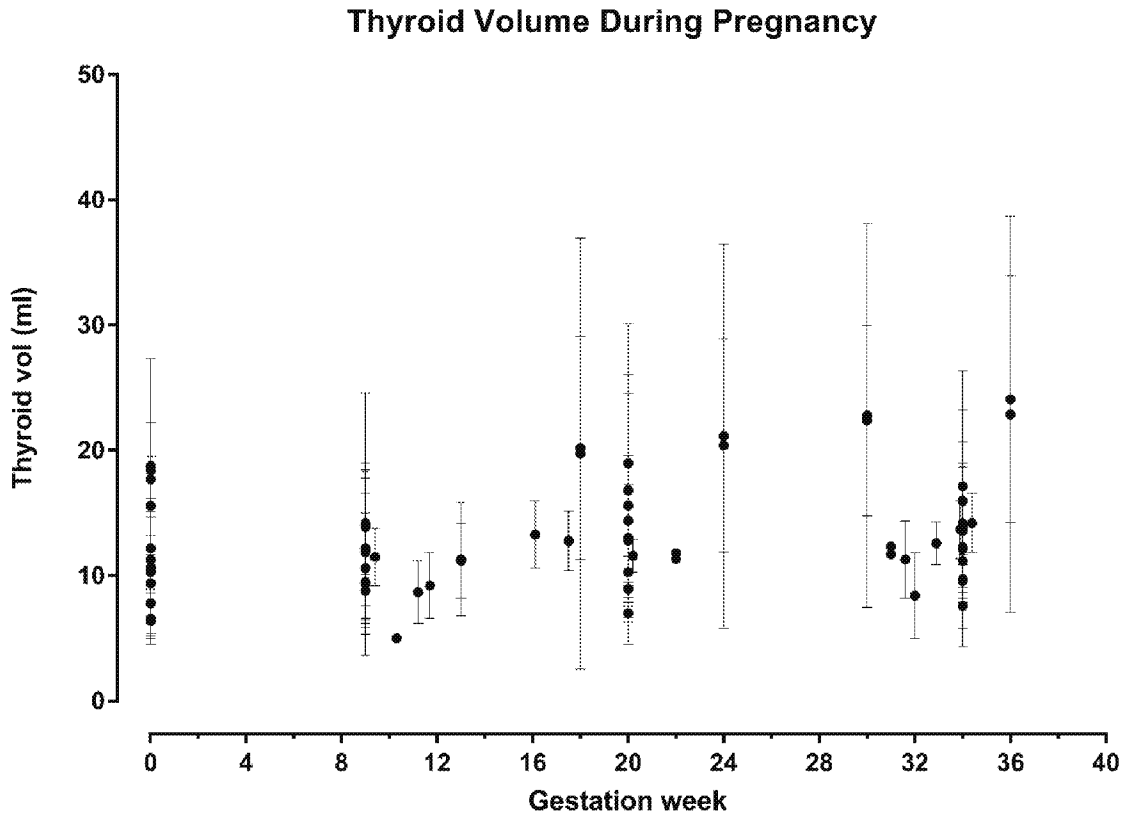
Figure A-29. Thyroid volume during pregnancy[a]



[a] (Data from Antonangeli et al., 2002; Azizi & Hedayati, 2002; Berghout et al., 1994; Brander & Kivisaari, 1989; Brucker-Davis et al., 2012; Fister et al., 2009; Gietka-Czernel et al., 2010; Glinoer, 1993; Glinoer et al., 1990; Glinoer et al., 1992; Gómez, Maravall, Gómez, Gumà, & Soler, 2000; Hegedüs et al., 1983; Jaén Díaz et al., 2008; Jaiswal et al., 2014; Kung, Lao, Chau, Tam, & Low, 2000; Liesenkötter, Göpel, Bogner, Stach, & Grüters, 1996; Rasmussen, Hornnes, & Hegedüs, 1989; Rasmussen, Hornnes, Hegedüs, & Feldt-Rasmussen, 1989; Rasmussen, Hornnes, Høier-Madsen, Feldt-Rasmussen, & Hegedüs, 1990; Sahin et al., 2014; Santiago et al., 2013; Sari, Balci, Altunbas, & Karayalcin, 2003; Smyth, 1999; Smyth, Hetherton, Smith, Radcliff, & O'Herlihy, 1997; Turcios et al., 2015; Vannucchi et al., 2017; Zygmunt et al., 2015).

Because of the lack of a gestation-age-dependent increase in the volume of the thyroid, the data during the 1st trimester was compared with the change in body weight during the 1st trimester to determine if it varied in proportion to body weight. Figure A-30 compares the body weight of women with the thyroid volume from non-pregnancy through the gestation week 16. The data were analyzed in Prism GraphPad by linear regression and a F-test to determine if slopes were significantly different for body weight versus thyroid gland volume (Table A-4). Because the change in weight and thyroid gland volume were similar over the 1st trimester, the thyroid gland volume was calculated as a constant fraction of body weight during the 1st trimester in the model.

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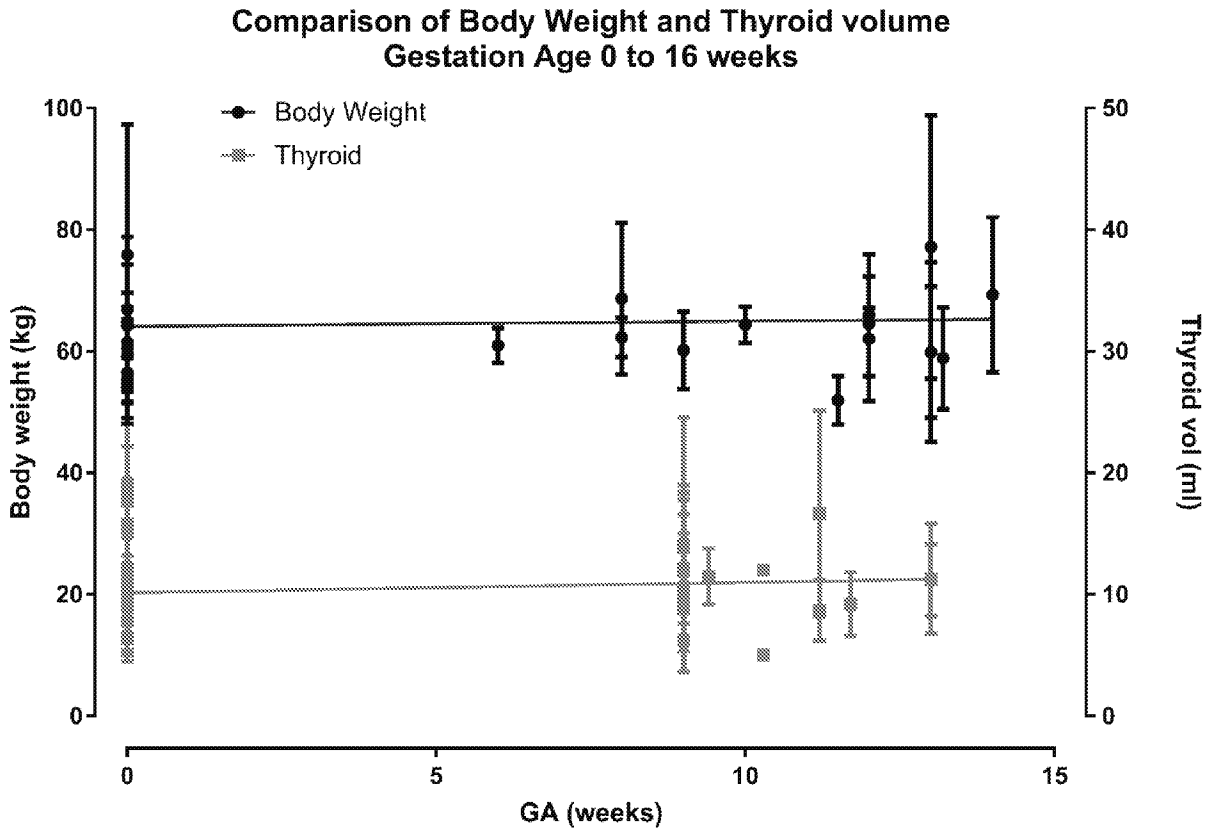
Figure A-30. Comparison of thyroid volume and body weight vs. gestational age (GA, weeks) up to 16 weeks of pregnancy[a]



[a] While both variables do not show a significant trend over this part of gestation, the regression lines show that they are parallel, hence that the ratio of thyroid volume to BW is constant. (Data from Antonangeli, et al., 2002; Azizi & Hedayati, 2002; Berghout, et al., 1994; Brander & Kivisaari, 1989; Brucker-Davis, et al., 2012; Fister, et al., 2009; Gietka-Czernel, et al., 2010; Glinoer, 1993; Glinoer, et al., 1990; Glinoer, et al., 1992; Gómez, et al., 2000; Hegedüs, et al., 1983; Jaén Díaz, et al., 2008; Jaiswal, et al., 2014; Kung, et al., 2000; Liesenkötter, et al., 1996; Rasmussen, Hornnes, & Hegedüs, 1989; Rasmussen, et al., 1990; Rezvanian et al., 2002; Sahin, et al., 2014; Santiago, et al., 2013; Sari, et al., 2003; Smyth, 1999; Smyth, et al., 1997; Turcios, et al., 2015; Vannucchi, et al., 2017; Zygmunt, et al., 2015).

To determine the fractional volume for the thyroid, the data from the pregnancy studies that reported both the thyroid and body weight during the 1st trimester were combined with values for non-pregnant women (Berghout, et al., 1994; Brander & Kivisaari, 1989; Brucker-Davis, et al., 2012; Gómez, et al., 2000; Hegedüs, et al., 1983; Jaiswal, et al., 2014; Sari, et al., 2003; Turcios, et al., 2015; Vannucchi, et al., 2017). A limited search was also conducted to identify a small set of papers that reported both thyroid volume and body weight in healthy women of reproductive age with normal BMIs. For pregnancy studies, values for the thyroid volume measure up to 16 weeks of gestation were used. The calculated fractional volumes of the thyroid from the various studies were used to determine an overall mean and distribution to use for the BBDR model by weighting the individual study values based on the number of subjects. The overall mean and SD for the fractional volume of the thyroid was 0.134 ± 0.054 mL/kg.

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Information on volumetric flow to thyroid during pregnancy was not found during the literature search. Only a few reports addressing intra-thyroidal blood flow velocity during pregnancy were identified (Fister et al., 2006; Fister, et al., 2009). In the absence of data, the thyroidal blood flow (Qthy) was assumed to increase in proportion to the thyroid volume. From Leggett & Williams (1995), Table 1, Qthy is 1.5% of cardiac output (QC), with a range of 0.7-2.2%. This fraction (and range) was used to set the pre-pregnancy value of Qthy.

1.4.6 Distribution of iodide and perchlorate into Rest of Body (ROB)

The ROB compartment represents all tissues other than the thyroid. Blood flow to this compartment is therefore calculated as total cardiac output minus the flow to the thyroid.

The partition coefficient (PC) for transfer of iodine and perchlorate into the ROB is calculated as a weighted sum of the tissue-specific coefficients from the pregnancy perchlorate model of Clewell (2007), as adapted by U.S. EPA (2009). In particular, tissue-specific PCs are weighted by the corresponding tissue fractions, for all tissues other than the thyroid and circulating blood. However, skin and mammary gland express NIS, and the Clewell et al. (2007)/U.S. EPA (2009) model included a term for active transport of iodide and perchlorate into these tissues. At steady state, when concentrations are below transporter saturation (ignoring inhibition of the term by perchlorate), the actual tissue: blood ratio, or effective partition coefficient for a given tissue is just:

$$PC_{eff} = PC + Vmax_{tissue,ligand}/(Km_{tissue,ligand} \cdot PA_{tissue,ligand})$$

where PC is the partition coefficient in the absence of transporter, $Vmax_{tissue,ligand}$ and $Km_{tissue,ligand}$ are the Vmax and Km for NIS-mediated transport of the ligand into the tissue, and $PA_{tissue,ligand}$ is the permeability-surface-area product for diffusion between the tissue and blood. Since both the Vmax and PA are assumed to scale as $BW^{0.75}$, that scaling cancels out and the PC_{eff} can be calculated using the scaled values of these parameters; i.e., the VmaxC and PAC. Therefore, PC_{eff} for perchlorate and iodide in skin and mammary gland are calculated this way for use in calculation of the overall ROB PC values. The resulting ROB PCs are approximately 20% higher for iodide and 80% higher for perchlorate than obtained without the term.

The resulting ROB: blood PCs are 0.243 and 0.558 for iodide for perchlorate, respectively. In particular, PC_{eff} for perchlorate in skin and mammary is 5.2 times higher than the corresponding PC.

This analysis does not explicitly account for NIS expression in the placenta or accumulation in the fetus which begins later in the first trimester. However, the remaining maternal body mass, in particular the fraction treated as skin and mammary gland, would be reduced. So unless the NIS expression in the placenta or iodide storage in the early fetus are much higher (e.g., 10 times) per kg mass than the average storage in all other maternal tissues combined, there should be minimal error from not including them as separate model compartments.

1.4.7 T3 and T4 Volume of Distribution

Data comparing T4 distribution in pregnant vs. non-pregnant women are provided by Dowling, Appleton & Nicoloff (1967), while data for non-pregnant women from Fisher, Oddie & Thompson (1971) and subjects of unspecified gender from Nicoloff, Low, Dussault & Fischer (1972) were also analyzed.

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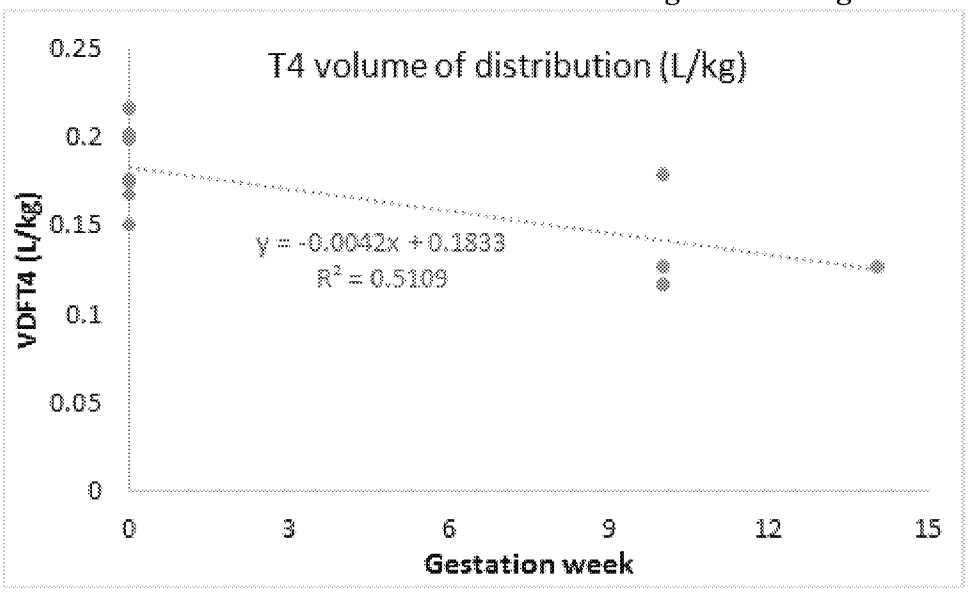
T4: For non-pregnant women the volume of distribution of T4 per kg BW (VDFT4) from Dowling et al. (1967) is 0.183 ± 0.023 L/kg (mean ± SD), from Fischer et al. (1971) is 0.154 ± 0.026 L/kg (mean ± SD), and from Nicoloff et al. (1972) is 0.166 ± 0.044 L/kg (mean ± SD), while Inada et al. (1975) reported a total volume of 8.7 ± 1.9 L (mean ± SD) from 5 men "adjusted to 60 kg body wt." Thus the VDFT4 from Inada et al. (1975) is interpreted as 0.145 ± 0.032 L/kg (mean ± SD). It can be noted that the VDFT4for male subjects from Fischer et al. (1971), 0.156 ± 0.016 L/kg (mean ± SD), was almost identical to that of female subjects, despite the men being an average of 23 kg heavier. The average of the mean VDFT4 from the four studies is: VDFT40 = 0.162 L/kg.

Data for up to 3.5 months of pregnancy from Dowling et al. (1967) were analyzed for gestation dependence, and appear to be roughly linear, as shown in Figure A-31. Since the initial value (intercept) of the regression was higher than the non-pregnant average estimated in the preceding paragraph, the slope was normalized to the regression intercept to obtain a fractional decline per gestation week: -0.0023/week. Thus VDFT4 during gestation is defined as:

VDFT4(GA) = 0.162*(1 – 0.023*GA) (L/kg).

Figure A-31. Variation in T4 volume of distribution with gestational age[a]



[a] Data from Dowling et al. (1967) were fit with a linear regression.

T3: From Nicoloff et al. (1972), VDFT3 in adults was calculated to be 0.548 ± 0.119 L/kg (mean ± SD). Fisher et al. (1971), citing Oddie, Fisher, Dussault & Thompson (1971), state that a volume of distribution of 34.8 L was found. Assuming the same average BW for all subjects in Fisher et al. (1971), this corresponds to VDCT3 = 0.491. Inada et al (1975), using a 3-compartment model analysis, obtained a total VDT3 = 46.6 ± 12.8 L (mean ± SD) in normal subjects, "adjusted to 60 kg body wt," which is interpreted as 0.777 ± 0.213 L/kg (mean ± SD). While the VDT3 from Inada et al. (1975) appears excessively high, above the range of 35-45 L given in the review by Distefano & Fisher (1976), with only two other primary sources considered it was not excluded, and the average among these three sources is VDFT30 = 0.6035 L/kg.

Since no data on change in VDCT3 with pregnancy is available, it is assumed to decrease in proportion to the decrease in VDFT4 described above, so:

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VDFT3(GW) = 0.603*(1 – 0.0023*GW) (L/kg)

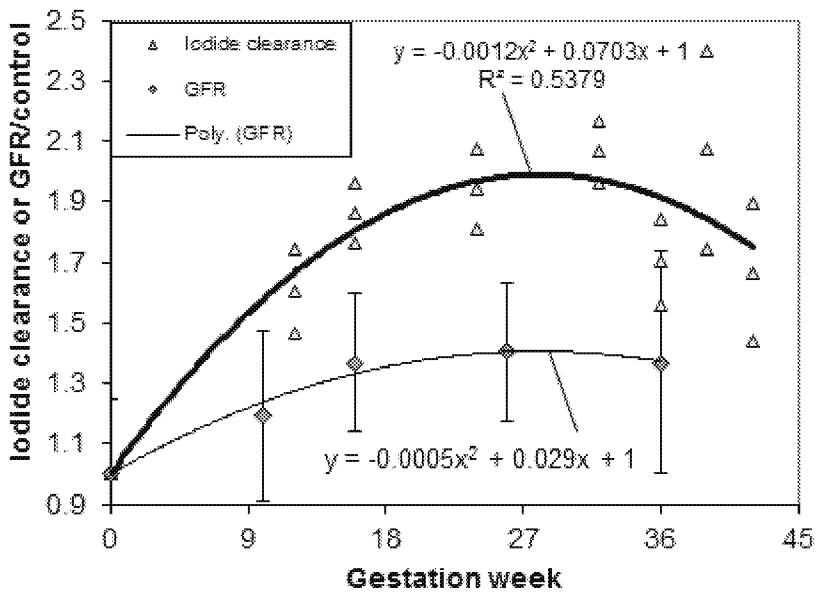
1.4.8 Renal Clearance

Figure A-32 shows glomerular filtration rates (GFR) from the Abduljalil et al. (2012) database and iodine urinary clearance rates reported by Aboul-Khair et al. (1964), each normalized to non-pregnant controls. While the GFR and urinary iodide clearance variation with weeks of pregnancy have the same shape, the fold-increase in iodine clearance is greater. Since clearance may not vary in direct proportion to GFR and Aboul-Khair et al. (1964) measured iodine clearance directly, the equation shown is used to multiply the base-line (non-pregnant) clearance rate for iodide in the 1T model:

$$CLR_{iodide}(GW) = (1 + 0.0703 \cdot GW - 0.0012 \cdot GW^2) \cdot CLR_{0,iodide} \cdot BW_0^{0.75},$$

$CLR_{0,iodide}$ is estimated as described in Section 0 using data from Greer et al. (2002) for non-pregnant women and BW_0 is the pre-pregnancy body weight.

Figure A-32. Variation in iodine clearance and glomerular filtration rate (GFR) during pregnancy[a]



[a] GFR data are from Abduljalil et al. (2012) database and iodine urinary clearance data are from Aboul-Khair et al. (1964). Data are shown as (value during pregnancy)/(value in non-pregnant control), to provide the relative change during pregnancy. The quadratic regression curves were therefore constrained to have a value of 1 at gestation week = 0 since clearance should equal that in non-pregnant women at the onset of pregnancy.

For perchlorate, the analysis of the Greer et al. (2002) data in Section 1 yielded a maximum likelihood scaled clearance constant, $CLRC_{0,perchlorate}$ = 0.133 L/h/kg$^{0.75}$. From Abduljalil et al. (2012), an average glomerular filtration rate (GFR) in non-pregnant women is 6.84 L/h, and the average mass for a non-pregnant woman is 61.1 kg, corresponding to a scaled clearance constant of 0.313 L/h/kg$^{0.75}$. Thus the observed clearance of perchlorate in non-pregnant women is less than ½ the GFR. However, as shown in Figure A-32 the observed fold-increase in iodine clearance during pregnancy is double what would be predicted based on GFR. The lack of correlation between GFR and iodine clearance is discussed further by Abduljalil et al. (2012) and in U.S. EPA (2009). Iodine

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and perchlorate clearance likely represent a balance between glomerular filtration and nonspecific fluid resorption, so changes in the resorption could account for this discrepancy.

Given that perchlorate has the same charge and similar ionic radius to iodide, and that the observed clearance in non-pregnant women is significantly less than GFR (though the model accounts for perchlorate binding to serum proteins), it seems reasonable to assume that the relative change (fold-increase) for perchlorate during pregnancy is the same as iodide. To be clear, $CLR_{0,perchlorate}$ and $CLR_{0,iodide}$ are not assumed to be the same; they are calibrated to the Greer et al. (2002) data which provide distinct values for the two ions. But the same multiplicative term is assumed to apply for the fold-increase in perchlorate clearance during pregnancy.

To evaluate the impact of this uncertainty, model simulations were conducted with perchlorate clearance during pregnancy estimated using the iodide-based equation or using the equation fit to GFR in Figure A-32, and the impact on predicted fT4 was less than 1%. For example, given an exposure to 150 μg/kg/d perchlorate to a 10th percentile woman ingesting 66.9 μg/d iodine (a high-risk individual), the fT4 level predicted at GW 16 is 5.83 pM assuming clearance varies in proportion to iodide and 5.78 pM assuming it varies in proportion to GFR.

Because the majority of T3 and T4 clearance occurs in the feces, rather than the urine, their clearance rates were not adjusted for changes in GFR. However, the rates of clearance were assumed to depend on the concentration of free hormones in serum, hence are affected by changes (declines) in the ratio of free to total hormone levels.

1.4.9 Free T4: T4 and free T3: T3

A number of studies were identified that measured free and total T4 at different time-points during pregnancy. However, because the current model is focused on the changes in the first trimester, the studies which could best inform this time-period were selected. It is assumed that at the time of conception the fT4:T4 ratio is that of an average non-pregnant woman, and therefore studies which report these levels in both non-pregnant women and at any time point in the first trimester were evaluated. Studies which did not report levels in non-pregnant women, but did so for at least 3 time-points no later than gestation week 16 were also evaluated, with the assumption that a regression using those time-points could be extrapolated back to the moment of birth.

Since most studies grouped subjects being sampled over multiple weeks for statistical analysis, the resulting value for fT4/T4 was associated with the middle of the range, e.g., data from subjects collected for "9-10 weeks" was treated as occurring at week 9.5. If a data group is indicated as ">6-12 weeks" (with the previous group indicated as including week 6), the average of 7 and 12, or 9.5 weeks was used to represent the data point.

Data with time-points specified this way were evaluated. Distribution statistics are generally reported separately for fT4 and T4. Therefore, the ratio of fT4/T4 was calculated preferentially from the reported mean values of fT4 and T4 for each gestation age range (or non-pregnant women). If the mean value was not reported, then the median or 50th percentile values were used instead.

An initial analysis of these ratios indicated a linear decline in the ratios with gestation week, but when that relationship was used in the model it was found to poorly fit the separate total T4 and fT4 data, which included many studies for which ratios were not available (results not shown). Therefore, the

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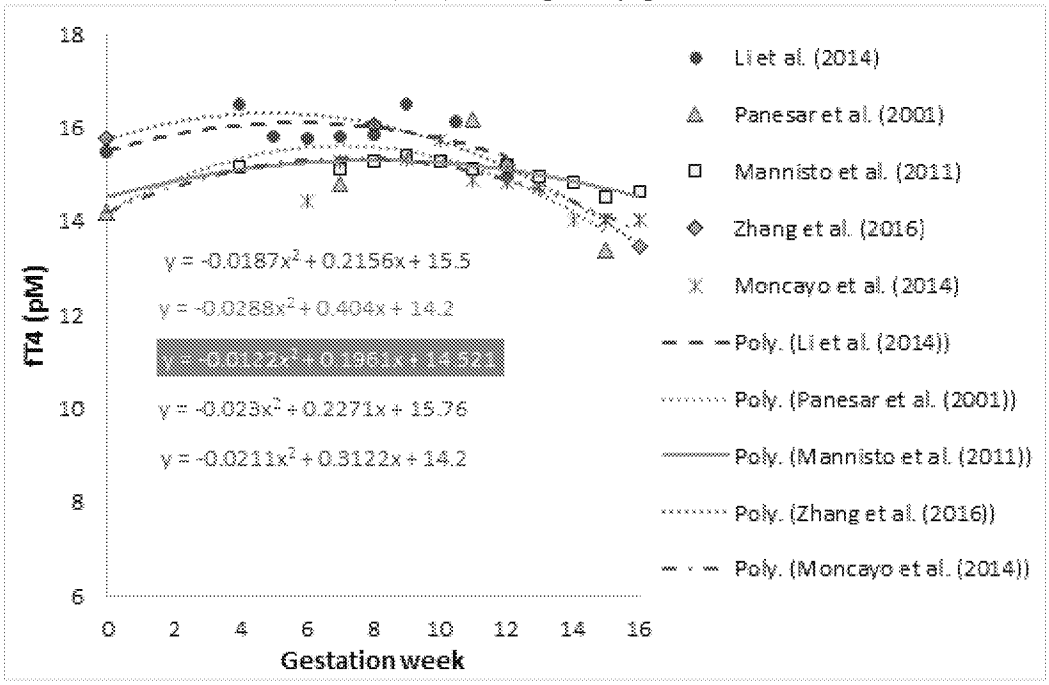
time-dependence of fT4 and total T4 were analyzed separately, to better estimate the ratio time-dependence.

Five studies were selected for analysis of fT4 with time because they reported multiple time points at GW ≤ 16 (Li et al., 2014; Männistö et al., 2011; Moncayo, Zanon, Heim, Ortner, & Moncayo, 2015; Panesar, Li, & Rogers, 2001; X. Zhang et al., 2016). The corresponding data, up to gestation week 16 (early 2nd trimester), are shown in Figure A-33, since data for weeks 15 and 16 appeared consistent with the first trimester data. The general pattern shown by the data is that fT4 initially increases until ~ GW 9-11, after which it declines. Therefore, a quadratic curve was fit to each set. For studies with data from non-pregnant women, treated as occurring at GW = 0, the quadratic curve was constrained to match that value exactly. Given the number of data from Männistö et al. (2011) and the fact that the unconstrained curve gave an intercept among the measured values, the GW = 0 value for this data set was taken to be the estimated y-intercept (constant value). For Moncayo et al. (2015) the y-intercept (constant) came out much lower than the other studies, 12.3 pM. Since this did not appear consistent with the remaining data, and this study did not report results for GW < 6, making the estimate more unstable, the intercept was constrained to match the lowest of the values from the other studies, the non-pregnant value from Panesar et al. (2001), 14.2 pM.

Figure A-33. Variation in free T4 (fT4) during early gestation[a]



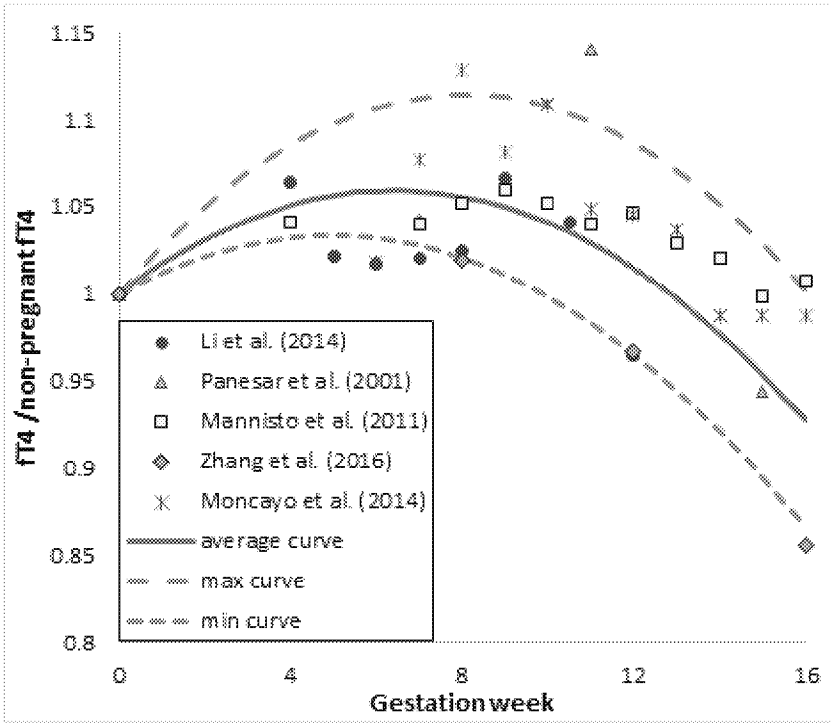
[a] A separate quadratic regression was performed for each data set. Regressions were unconstrained except for fitting Moncayo et al. (2015), where the intercept was set equal to the control value from Panesar et al. (2001), as explained in the text. Other data shown are from Li et al. (2014), Männistö et al. (2011) (Männistö, et al., 2011), and Zhang et al. (2016).

Since a function adjusting the fT4/T4 ratio is applied as a relative change vs. the ratio in non-pregnant women, these data were then normalized to the corresponding GW = 0 values, shown in Figure A-34. The parameters were analyzed as follows, give then general form, $a \cdot x^2 + b \cdot x + c$:

1) each value of b was normalized to c (b/c) and the average, maximum, and minimum of those values calculated, boc_{mean}, boc_{min}, boc_{max};
2) each value of a was normalized to b (a/b) and the average, maximum, and minimum of those calculated, aob_{mean}, aob_{min}, aob_{max};
3) the curve was represented as $aob \cdot boc \cdot GW^2 + boc \cdot GW + 1$ for comparison to the normalized data, using corresponding mean, min, and max parameters.

The set of curves in Figure A-34 appears to capture most of the variability in the data, hence should adequately represent the time-dependence in fT4, in evaluating variation of fT4/T4. The curves are generally denoted $fT4_{quad}(GW)$.

Figure A-34. Variation in fT4 normalized to non-pregnant levels during early gestation[a]



[a] Data sources given in legend of Figure A-33. See preceding text describing derivation of regression and bounding curves.

To estimate the relative change in T4 with gestation, data from 5 studies which reported both non-pregnant controls and values for GW ≤ 16, (La'ulu & Roberts, 2011; Soldin, 2004; Rt. Stricker et al., 2007; Y.Q. Yan et al., 2011; X. Y. Zhang, B.; Li, C.; et al., 2016) and were normalized to the non-pregnant value and shown in Figure A-35. As the resulting change with gestation appeared sigmoidal a single Hill equation was fit to the combined normalized data, $T4_{Hill}(GW)$.

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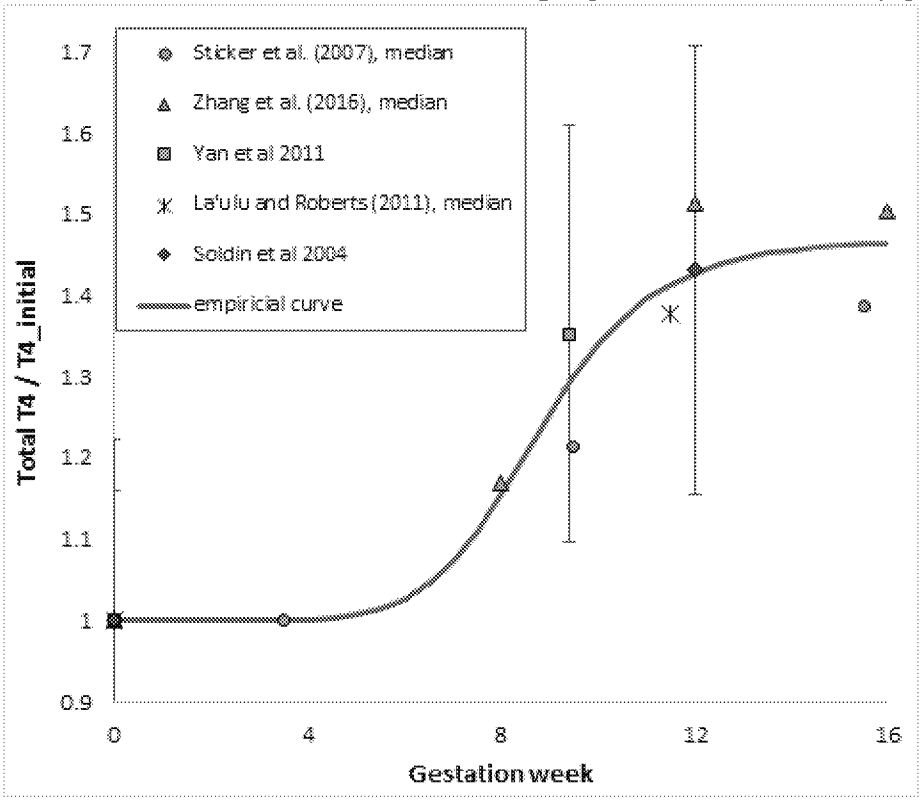
Figure A-35. Variation in total T4 relative to non-pregnant controls in early gestation[a]



[a] The empirical curve is a Hill equation fit to the collected data from (The empirical curve is a Hill equation fit to the collected data from La'ulu & Roberts, 2011; Soldin, 2004; Rt. Stricker, et al., 2007; Y.Q. Yan, et al., 2011; X. Y. Zhang, B.; Li, C.; et al., 2016)

The empirical frT4 = fT4/T4 ratio is then assumed to vary from the non-pregnant value, $frT4_0$ as $fT4_{quad}(GW)/T4_{Hill}(GW)$; i.e.

$$frT4 = frT4_0 * fT4_{quad}(GW)/T4_{Hill}(GW),$$

where $frT4_0$ can vary between studies or individuals, and $fT4_{quad}(GW)$ varies based on the choice of parameters aob and boc as shown above.

Since the change in bound/free is assumed to be determined by changing levels of serum binding globulins, which also apply to fT3/T3 ratios, the same variation with GW is assumed for fT3/T3:

$$frT3 = frT3_0 * fT4_{quad}(GW)/T4_{Hill}(GW),$$

but with $frT3_0$ defined by data for that ratio in non-pregnant women from various studies or individual data.

To evaluate how well the resulting fTx/Tx ratios compare to the empirical data, data from La'ulu & Roberts (2011), Medici et al. (2012), Soldin et al. (2004), Stricker et al. (2007), Yan et a. (2011), and Zhang et al. (2016). Soldin et al. (2004) did not report values for fT3 and T3.) Initial values ($frT4_0$) were selected to match the highest, lowest, or mean value for non-pregnant women from these studies. The upper value of $frT3_0$ was estimated by linear regression of the Stricker et al. (2007), extrapolated to GW = 0, and the lower value of $frT3_0$ from data for non-pregnant women from Roef et

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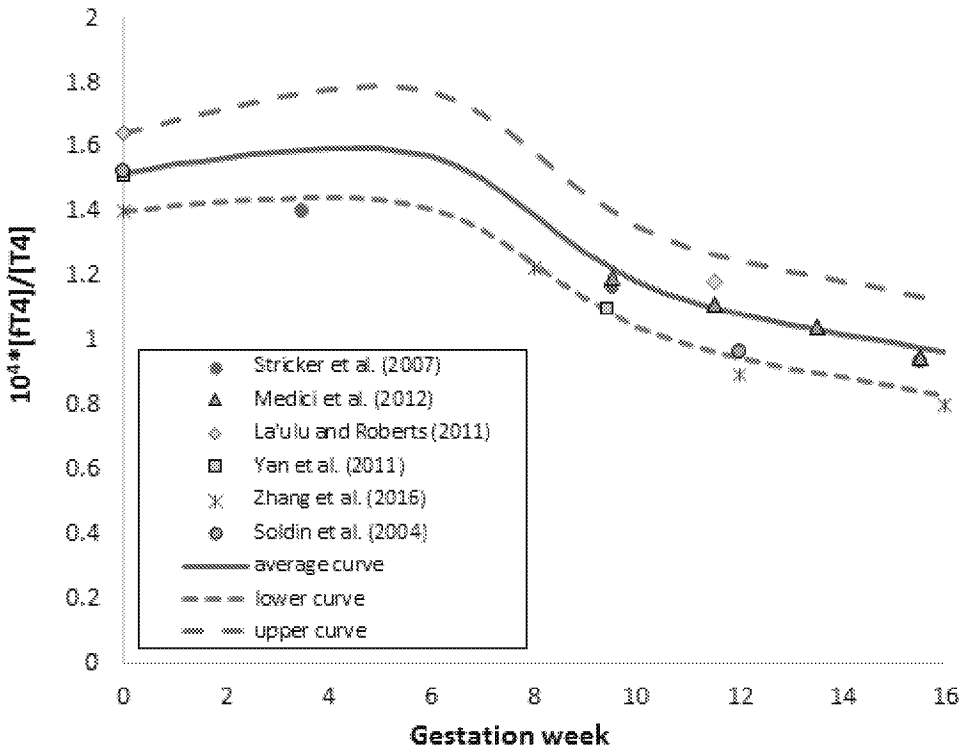
al. (2013). This was the lowest value among ratios calculated for several which reported both fT3 and T3 in non-pregnant women, except for a slightly lower value that occurred among women specifically coded as taking oral contraceptives. For the upper curve the upper quadratic curve values for $frT4_{quad}$ were used, for the mean, mean $frT4_{quad}$, and for the lowest, min $frT4_{quad}$. The resulting empirical curves and data are shown in Figure A-36 and Figure A-37 and appear to capture the resulting time-dependence and variation in fTx/Tx ratios fairly well.

Figure A-36. Ratio of fT4 to T4 during early pregnancy[a]



[a] Data sources given in legend of Figure A-33. The average, lower, and upper curves are defined by the ratio of separate curves for fT4 and T4, as described in the text.

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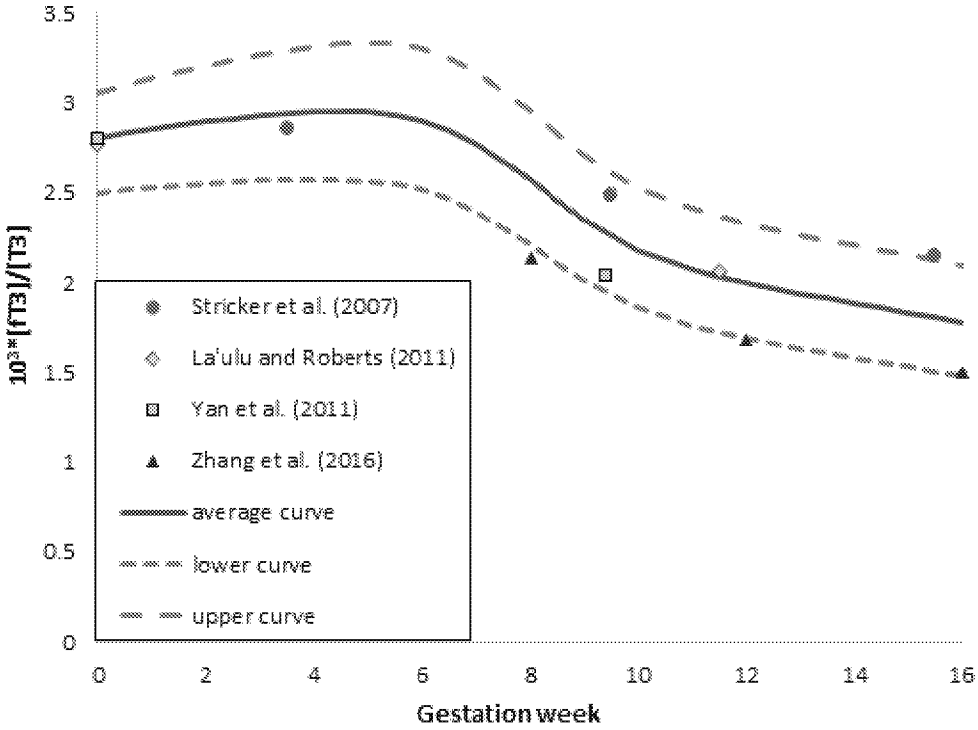
Figure A-37. Ratio of fT3 to T3 during early pregnancy[a]



[a] Data sources given in legend of Figure A-33. The average, lower, and upper curves are defined by the ratio of separate curves for fT4 and T4, as described in the preceding text, but with values at the start of pregnancy (gestation week = 0) set using data for free and total T3 as described in the preceding text.

1.4.10 Variation in T4 and T3 levels and production – data for model evaluation

A number of studies have shown increases in total T4 in the range of 40-50% in the first trimester compared to non-pregnant women, or weekly variation within that trimester consistent with such an increase, and a similar or slightly lower increase in total T3 (La'ulu & Roberts, 2011; Medici, et al., 2012; Soldin, 2004; R. Stricker, et al., 2007; Y. Q. Yan, et al., 2011; X. Zhang, et al., 2016), as shown in Figure A-38 and Figure A-39. (Time-points (specific weeks for plotting data) were identified for each measurement as described in "Free T4:T4" above.) This increase is understood to be driven by increasing levels of human chorionic gonadotropin (hCG) produced by the placenta. Since T4 is metabolized to T3, the increase was initially assumed to result from increasing T4 production. If necessary, the production rate constant for T4 could be multiplied by a function of gestation age adjusted to match the normal increase in T4 over the first trimester, but based on the results shown below, this correction appears not to be necessary. Model predictions for T3, which are also expected to increase, are compared to observed changes in its level. If the model does not predict an increase in T3 as high as is observed, then the T3 production rate can be further adjusted to match those data.

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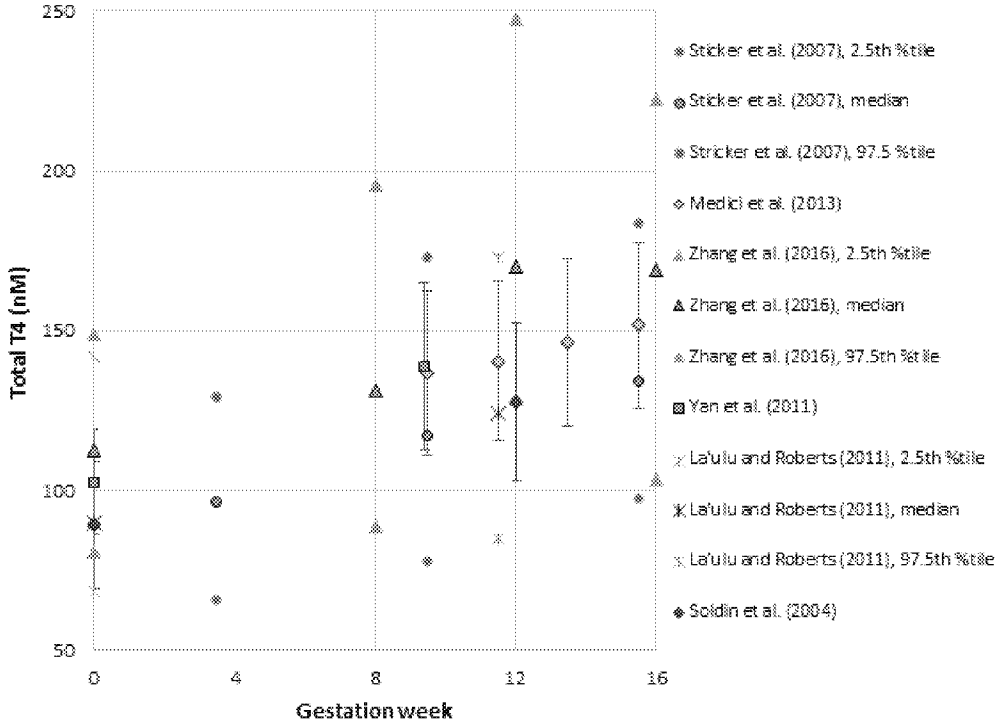
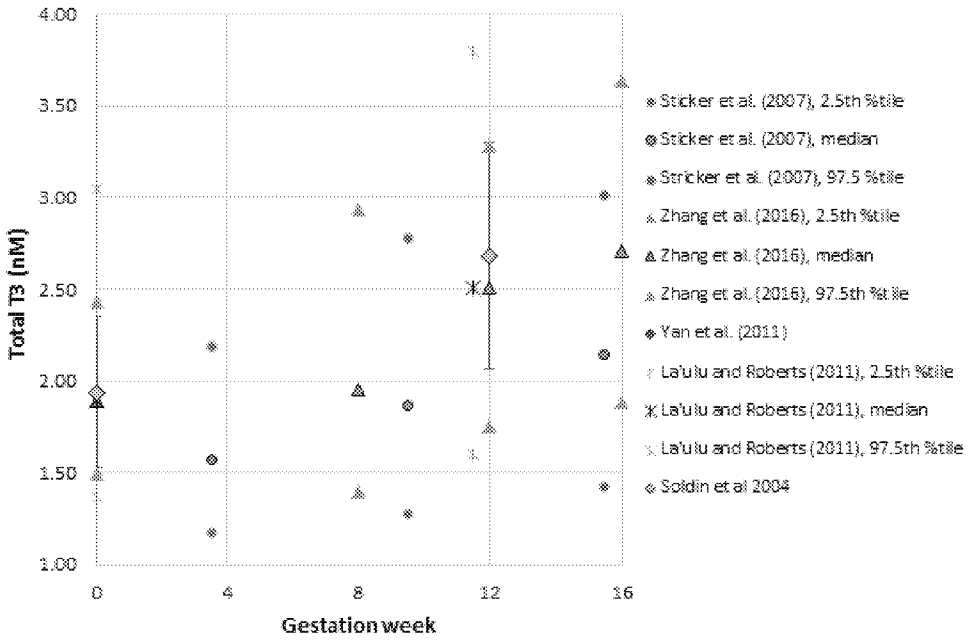
Figure A-38. Total T4 levels during pregnancy[a]



[a] (La'ulu & Roberts, 2011; Medici, et al., 2012; Soldin, 2004; R. Stricker, et al., 2007; Y. Q. Yan, et al., 2011; X. Zhang, et al., 2016).

Figure A-39. Total T3 levels during pregnancy[a]



[a] (La'ulu & Roberts, 2011; Medici, et al., 2012; Soldin, 2004; R. Stricker, et al., 2007; Y. Q. Yan, et al., 2011; X. Zhang, et al., 2016).

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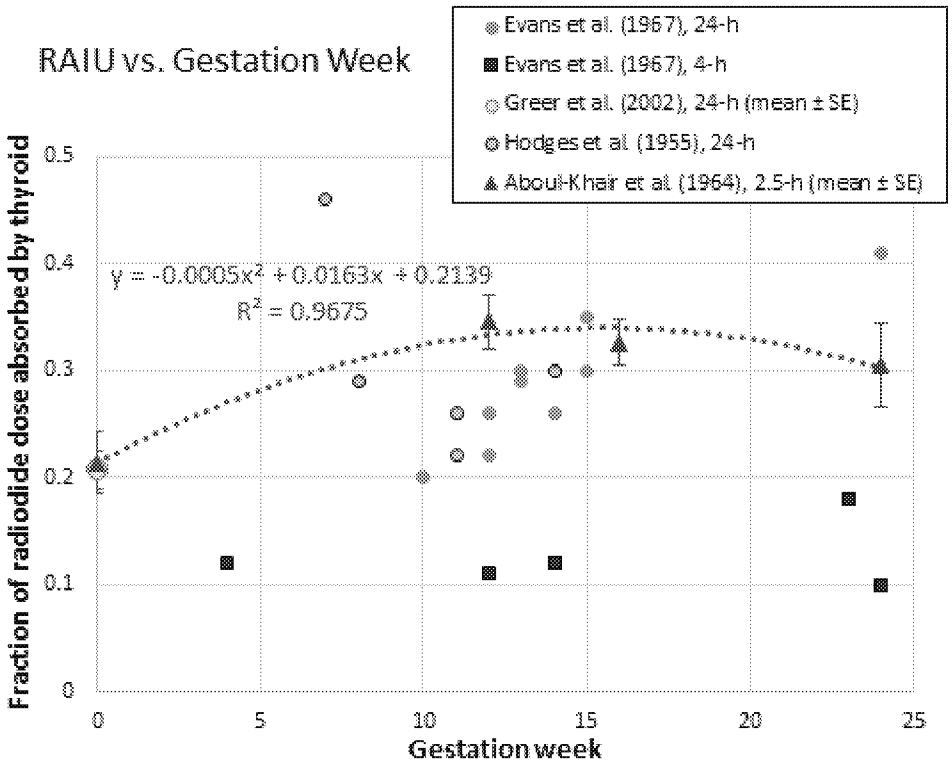
1.4.11 Variation in NIS, Vmax for thyroidal uptake of iodide during pregnancy

Treating data for the 22-46 year-old women from Greer et al. (2002) as occurring at the start of pregnancy, those results are then compared to RAIU measured at different points in pregnancy by Aboul-Khair et al. (1964), Evans, Kretzschmar, Hodges, & Song (1967), and Hodges, Evans, Bradbury, & Keettel (1955) in Figure A-40. These include data for 4-h RAIU from Evans et al. (1967), while the data from Aboul-Khair, et al. (1964) are for 2.5-h uptake. (Data from Evans et al. (1967) and Hodges et al. (1955) are individual measurements.)

While most the pregnancy values are in the same range as the non-pregnant women from Greer et al. (2002), it must be noted that only Aboul-Khair, et al. (1964) measured RAIU in non-pregnant controls, and observed a clear, significant increase in uptake during pregnancy. This is consistent with the observation that T4 and T3 levels are higher during pregnancy (e.g., Soldin, Tractenberg, & Soldin, 2004). Therefore, the regression curve fit to the data of Aboul-Khair, et al.(1964) is used, noting that it is only applied up to GW = 16. When normalized to the value at GW = 0, the equation becomes:

$$VCHNG(GW) = 1 + 0.076 \cdot GW - 0.0025 \cdot GW^2.$$

Figure A-40. Variation in radioiodide uptake during early gestation[a]



[a] Only Aboul-Khair et al. (1964) reported RAIU in both pregnant women and non-pregnant controls, allowing for a clear evaluation of the pregnancy-related change. Other data are from Evans et al. (1967), Greer et al. (2002) (22-46 year-old subjects), and Hodges et al. (1955).

1.4.12 Increase in hCG with Gestation

Median values for human chorionic gonadotropin (hCG) vs. gestation week were taken from Korevaar et al. (2015), Table 1, and are shown in Figure A-41. The first value was indicated as

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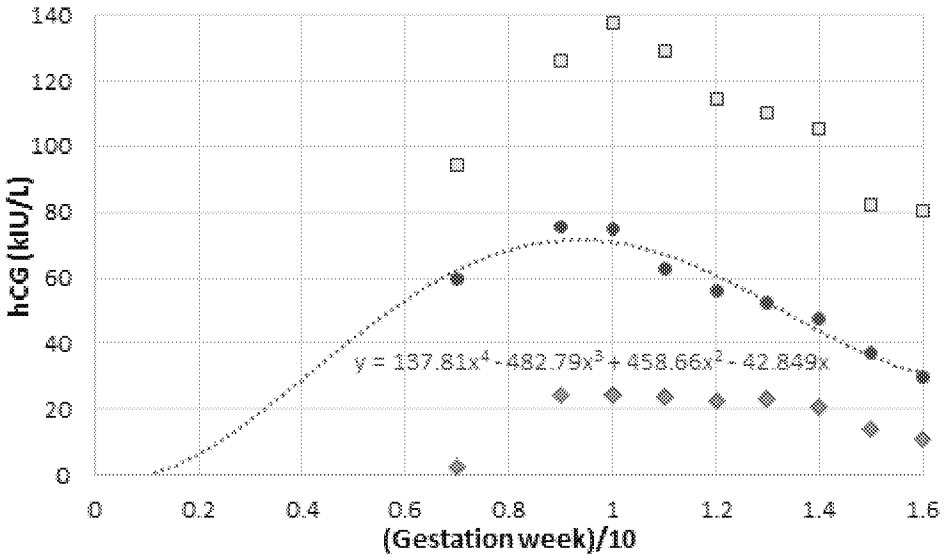
representing GW < 9. Since the first individual data point shown in Figure 1 of the paper appears to be marked ~ GW 4, and only a few (out of 32) data points in this time-range are shown between that and GW ~ 6, the corresponding hCG level was assumed to occur at GW 7. The data are plotted against (Gestation week)/10 so that the coefficients of the fourth order polynomial fit to the median data can be read to 5 significant figures. When the polynomial becomes negative, prior to ~ GW 1, hCG is set = 0.

Figure A-41. Variation in human chorionic gonadotropin (hCG) during early pregnancy[a]



[a] Data are from Korevaar et al. (2015), 2.5th, median, and 97.5th percentiles.

The effect of hCG is explicitly assumed to be multiplicative to that of TSH on T3 and T4 production. (The variation in RAIU uptake, evaluated just above, is also likely due to hCG signaling, but is not treated as an explicit function.) The relationship between fT4 and hCG shown by Glinoer et al. (1997), Figure 5 (Lower Graph) is used as an estimate. The data from this plot were digitized and are shown in Figure A-42. Hence the rate constants for production of T4 and T3, are assumed to increase as the slope over the intercept, i.e., production is multiplied by:

$$HCG_{reg} = 1 + 0.00354*hCG,$$

and also by a term TSH_{reg} for the effect of TSH as described below.

While hCG might otherwise be assumed to also impact iodide uptake by the thyroid, a gestation-dependent adjustment described in the preceding section is already being applied. This variation is assumed to result from hCG regulation, so further adjustment of the Vmax explicitly as a function of hCG would be duplicative.

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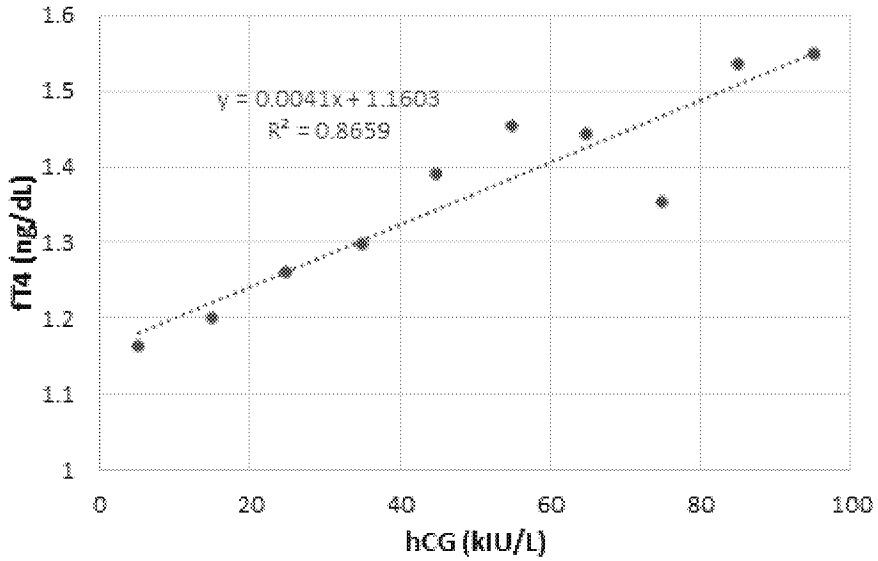
Figure A-42. Relationship between fT4 and hCG concentration during pregnancy[a]



[a] Data from Glinoer (1997).

1.4.13 Relationship Between TSH and fT4

Hadlow et al. (2013) analyzed the relationship between TSH and fT4 using data from over 150 thousand subjects, collected over a 12-year period, extracted from a larger set of clinical records after excluding, "patients thought likely to have factors confounding the physiological HPT axis response or resulting in analytical interference with thyroid function testing." They found that the relationship for the full population, which contained both men and women, could be described as a pair of sigmoid curves, with inflection points at 7.0 and 20.6 pM fT4:

$$\ln TSH = 1.36 + 3.5/[1 + exp(fT4 - 7.0)]; \quad fT4 \leq 12 \text{ pM}$$

$$\ln TSH = -3.67 + 5.34/[1 + exp((fT4 - 20.6)/3))]; \quad fT4 > 12.0$$

The authors (John Walsh, Suzanne Brown, personnel communication), provided to the U.S. EPA the summary data for the female subjects and a pair of equations of the same form were fit to the female data:

$$\ln TSH = A1 + B1/\{1 + exp[(fT4 - C1)/D1]\}; \quad fT4 \leq f0$$

$$\ln TSH = A2 + B2/\{1 + exp[(fT4 - C2)/D2)]\}; \quad fT4 > f0$$

The values of A2 and B2 were constrained such that the two portions of the curve *and* the slopes of the two curves matched at f0. Matching of the slope occurs by setting:

$$B2 = \frac{B1 \cdot (D2/D1) \cdot \{1 + exp[(f0 - C2)/D2)]\}^2 \cdot exp[(f0 - C1)/D1 - (f0 - C2)/D2]}{\{1 + exp[(fT4 - C1)/D1]\}^2}$$

Then the curve values are matched by setting:

$$A2 = A1 + B1/\{1 + exp[(f0 - C1)/D1]\} - B2/\{1 + exp[(f0 - C2)/D2)]\}.$$

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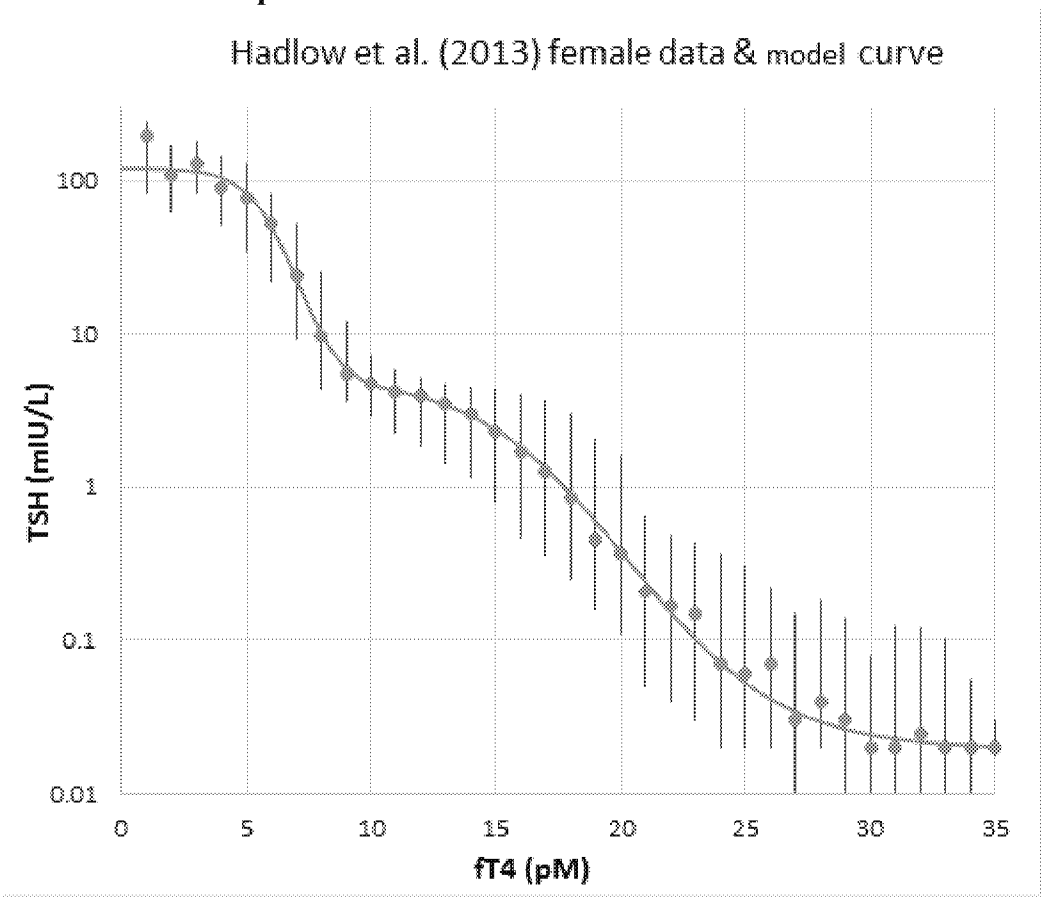
A total of 7 parameters were then adjusted: A1-D1, C2, D2, and f0. The model error vs. the data (median, with 25th-75th percentile shown in first plot below) were weighted by the interquartile range. Also, when the 2007-2012 NHANES data were evaluated as described above, all but one of the values were in the range 5-17 pM fT4. Therefore, the model error vs. data was weighted 10x higher for points in this range of fT4. The resulting model parameters are: A1 = 1.40, B1 = 3.40, C1 = 7.01, D1 = 0.971, A2 = -3.95, B2 = 5.66, C2 = 20.3, D2 = 3.05, with the f0 = 10.72. The resulting model fit is shown in Figure A-43.

Figure A-43. Relationship between TSH and fT4 with model curve



(Hadlow, et al., 2013)

However, when this relationship is compared to TSH vs. fT4 data from a number of studies which measured these at different time-points during pregnancy (Figure A-44), it is seen to over-predict most of the data.

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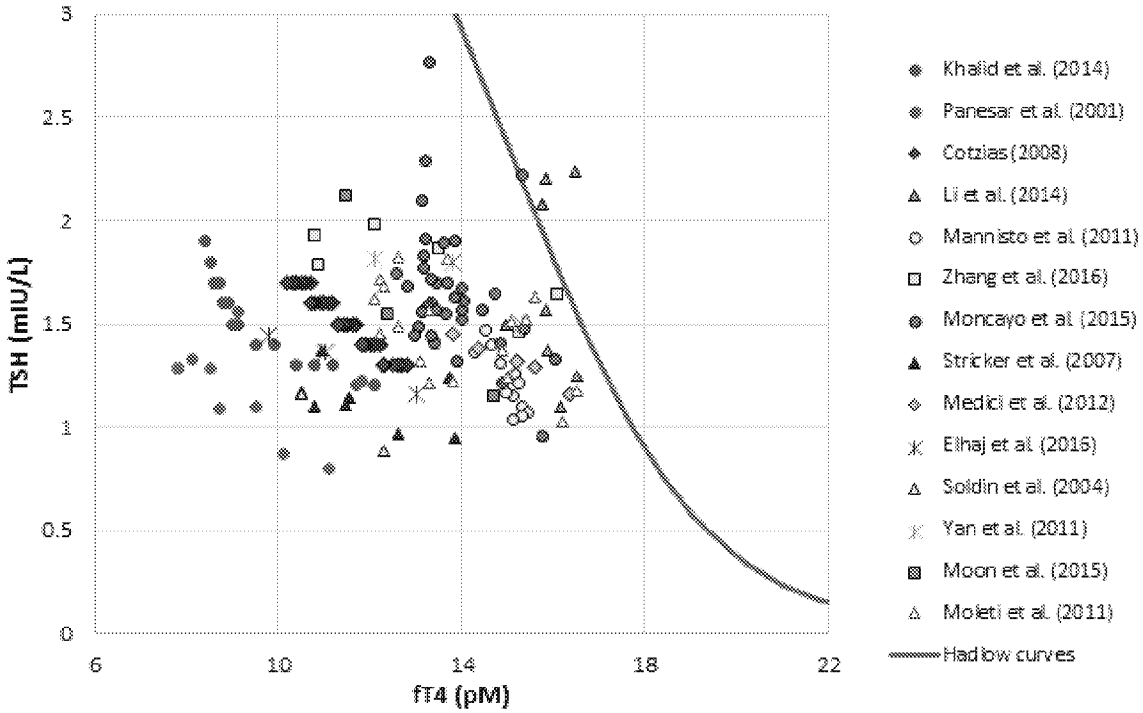
Figure A-44. Comparison of unadjusted Hadlow curve to TSH vs. fT4 data from various studies



(Cotzias, Wong, Taylor, Seed, & Girling, 2008; Elhaj, Adam, Ahmed, & Lutfi, 2016; Khalid et al., 2014; Li, et al., 2014; Männistö, et al., 2011; Medici, et al., 2012; Moleti et al., 2011; Moncayo, et al., 2015; Moon, Chung, Park, Hur, & Yun, 2015; Panesar, et al., 2001; Soldin, Tractenberg, Hollowell, et al., 2004; R. Stricker, et al., 2007; Y. Q. Yan, et al., 2011; X. Zhang, et al., 2016)

Considering the data shown here, while there is significant inter-study variability, each study does indicate a general negative trend, qualitatively consistent with the feedback mechanism (dencreased fT4 increases TSH). That the TSH levels measured are much lower than the Hadlow equation suggests, however, that fT4 during pregnancy is more effective or potent in reducing TSH than the curve, fitted to data for non-pregnant women, predicts. A possible mechanism for increased potency is that hCG has been shown to increase endothelial permeability (Rodewald et al., 2009), which could allow more fT4 to penetrate and act on the hypothalamus if the same mechanism occurs in that tissue. While data to specifically characterize such a mechanism are not available, a relatively simple solution for calibrating the Hadlow equation to a given data set is to use a multiplicative factor such that given an fT4-TSH pair ($fT4_0$, TSH_0; e.g., from non-pregnant controls), the curve is compressed to:

$$TSH = TSH_0 \cdot Hadlow(fT4)/Hadlow(fT4_0).$$

The results of compressing the curve this way using the TSH_0 = 1.36 mIU/L and $fT4_0$ = 10.31 pM, the median values obtained from NHANES 2007-12 data and described above, is shown in Figure A-45. The TSH curve is compressed by a factor of 0.3. With this correction it can be seen that the slope and nonlinearity in the Hadlow curve are roughly consistent with the various data sets. The alternative approach of scaling fT4 by a potency factor gave a result which, while centered in the data, had a slope far steeper than exhibited by the data sets in general (results not shown).

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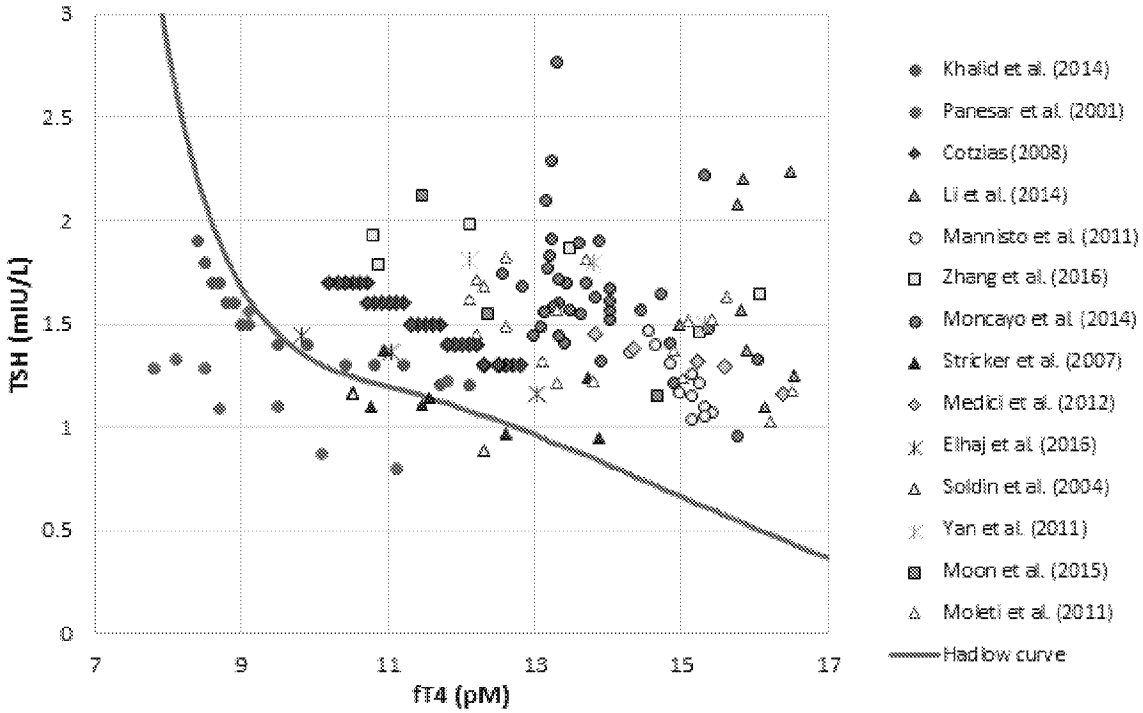
Figure A-45. Comparison of adjusted Hadlow curve to TSH vs. fT4 data from various studies[a]



[a] Data sources are listed in legend of Figure A-44.

Tuning the Hadlow TSH-fT4 curve to a particular data set (using TSH and fT4 in non-pregnant controls) should capture the primary fT4-TSH relationship observed. For example, an upper bound simulation can be conducted by setting $fT4_0$ and TSH_0 to the 97.5th percentiles of their respective distributions. Evaluation of the overall impact of this approach, and the assumed relationship between TSH and T4 and T3 production, occurs as part of evaluating total model predictions against gestational thyroid hormone data. Other realizations of the Hadlow curve plotted against TSH vs. fT4 data, are shown in Figure A-46 to give a sense of how the relationship scales.

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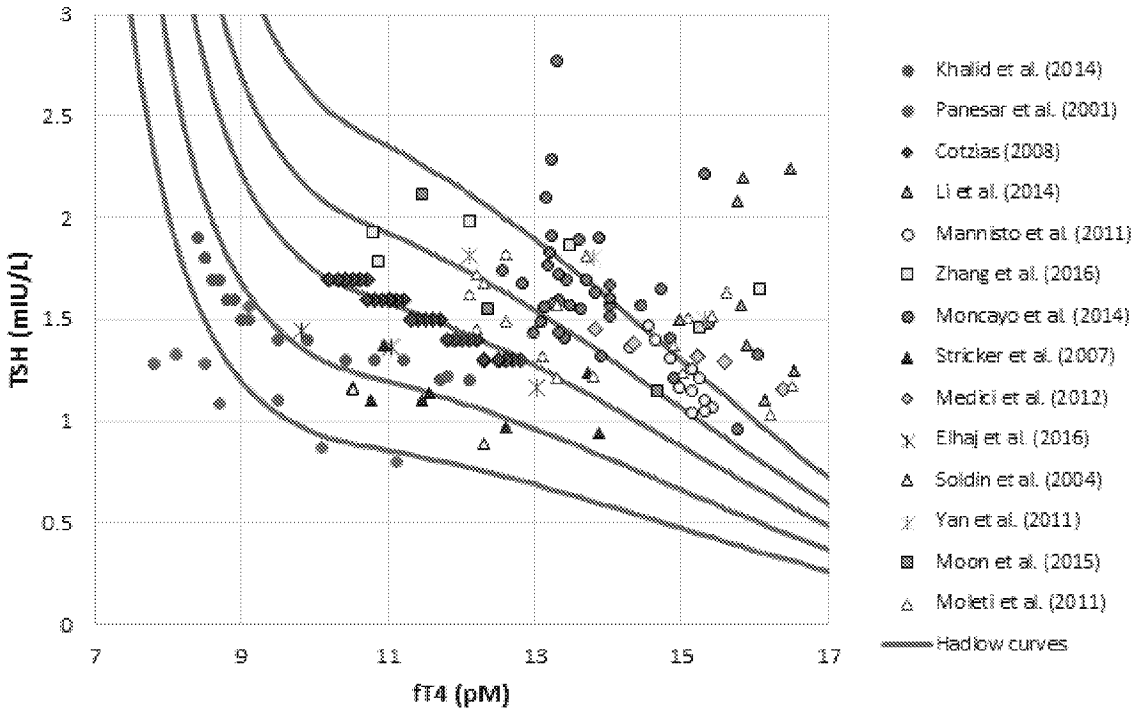
Figure A-46. Relationship between TSH and fT4 across multiple studies[a]



[a] The curves are roughly adjusted in this example to show the range of behavior. Data sources are listed in legend of Figure A-44.

The effect of TSH on thyroid function is assumed to vary in proportion to changes in TSH above and below $T4_0$; i.e., $TSH_{reg} = (TSH/TSH_0)^{pREG}$, where pREG is a tuning parameter. Evaluation of the model against the available data sets did not provide a clear indication that pREG was different from 1, except to the extent that the model was able to match NHANES data at low iodine intake. The NHANES data (described in more detail below in Section 2.2.2) do not show a clear correlation between TSH and fT4 (results not shown), so within that data set they vary independently. One could assume, therefore, that individuals with an average fT4 and high TSH have that combination because their thyroid has a weak response to TSH, and vice-versa. Therefore a lower and upper bound for pREG can be estimated as (median TSH)/(97.5th percentile TSH) = 0.398 and (median TSH)/(2.5th percentile TSH) = 3.09, respectively, with a median value of pTSH = 1. TSH_{reg} multiplies both the Vmax for iodide uptake and the rate constants for T4 and T3 production by the thyroid.

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2. Model Evaluation and Results

2.1 Perchlorate kinetics in non-pregnant women and in men

Because of time constraints for development of the BBDR model, the version of the model used in Section 1 was adapted from the model for lactating women described in U.S. EPA (2016), so that the analysis of those parameters could occur in parallel with development of the 1T BBDR model. Since the perchlorate sub-model is simplified in the 1T model, model predictions of perchlorate pharmacokinetics should be evaluated against existing data, using the parameters from Sections 1 and 1.3. Perchlorate PK data in adult humans are quite limited and no suitable data have been identified for pregnant women; i.e., measurements of perchlorate concentrations in human blood and/or urine for defined or known exposures, with blood concentrations being most important since this is what determines the effect level. Urinary biomarker data from spot samples are not adequate for such evaluation, since they represent a single time-point occurring during randomly fluctuating exposures and excretion events, and do not inform blood concentrations. The lack of perchlorate PK data in pregnant women is not surprising, given the hazard such experiments would have for the developing fetus.

The data sets available for evaluation of the 1T model (perchlorate sub-model) are those of Greer et al. (2002), used for calibration in Section 1, Durand (1938), Eichler (1929), and Kamm & Drescher (1973). Source values could not be obtained for the data shown in Figure 11 of Merrill et al.(2005), which identifies them as "unpublished data, Brabant and Leitolf." Given that the same (top) dose level and duration were as describe by Mattie (2000), i.e., 12 mg/k/d for 2 weeks, the average BW of the top dose group and division of dose into 3 events day ~ 6 h apart, was assumed. Data for the later three were available in model code (a .cmd file used in older versions of acslX software) obtained from Dr. Elaine Merrill (USAF, WPAFB, Ohio, personnel communication). The later data sets only provide the cumulative amount excreted in urine at various times after a single bolus dose, in each case by a single male subject.

Figure A-47 shows the time-course of predicted serum perchlorate concentrations in the non-pregnant woman for the highest two dose groups from Greer et al. (2002) (all but a few serum levels in lower dose groups were below the limit of detection). The model simulations are seen to match reasonably well to the average blood levels seen in the subjects, and the rate of clearance observed at the end of the study, characterized by the slope of the simulations, is well matched.

Figure A-48 shows the time-course of predicted serum perchlorate concentrations in an 84-kg woman vs. serum perchlorate data digitized from Figure 11 of Merrill et al. (2005), from 5 male subjects ingesting 12 mg/kg/d. 84 kg is the average BW of the 4 male subjects identified as receiving that dose in Mattie (2000) (which does not include serum perchlorate data). The model under-predicts the first time-points digitized, but it must be noted that the early time points are particularly sensitive to the timing of the serum measurement vs. the initial dose(s). The model matches the time-point at 7 days reasonably well, but if the 2.5th percentile of the distribution for median perchlorate clearance is used (red, thin curve) the agreement is slightly better. The predicted decline in serum concentrations at the end of dosing is be faster than the average observed (as also occurred for the PBPK of model of Merrill et al. (2005)), but the model is within 1 SD of the measured mean. The model is judged to adequately fit these data, given that the dose level is much higher than used for model calibration. Clearly the inter-individual variability is much greater than accounted for based on the uncertainty in the median perchlorate clearance, but that is to be expected.

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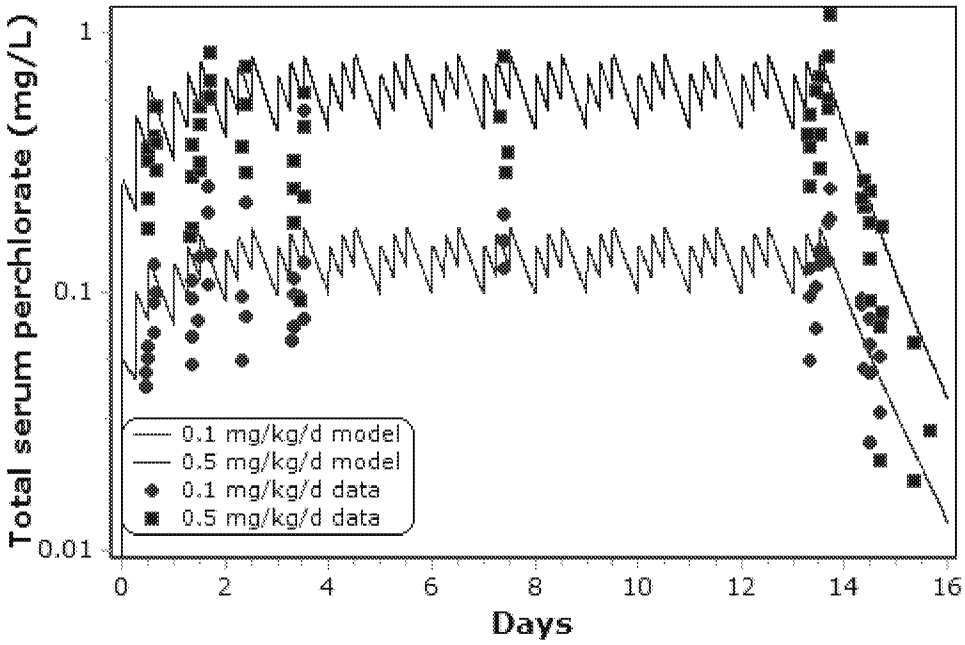
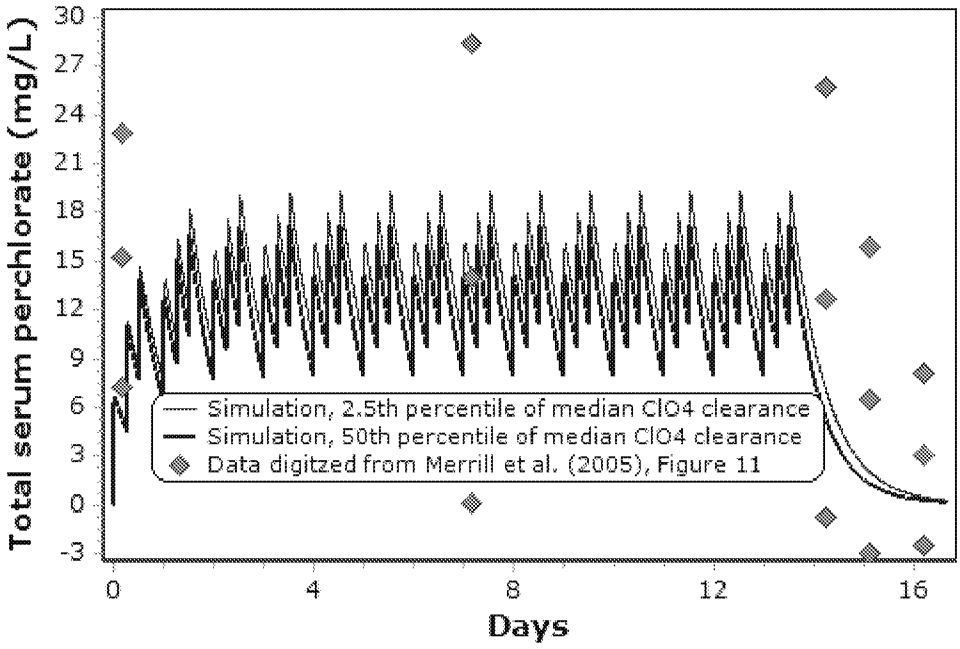
Figure A-47. Perchlorate sub-model predictions vs. Greer et al. (2002)[a]



[a] Data are for female subjects

Figure A-48. Perchlorate sub-model results vs. data from Merrill et al. (2005)[a]



[a] Data were digitized Figure 11 of Merrill et al. (2005) for 5 males ingesting 12 mg/kg/d perchlorate, divided into 3 doses per day; points are mean ± SD at each observation time. Simulations are for an 84 kg adult using either the 50th or 2.5th percentile of the distribution for median perchlorate clearance. Thus the difference represents uncertainty in the median, not the range expected among all individuals in the population.

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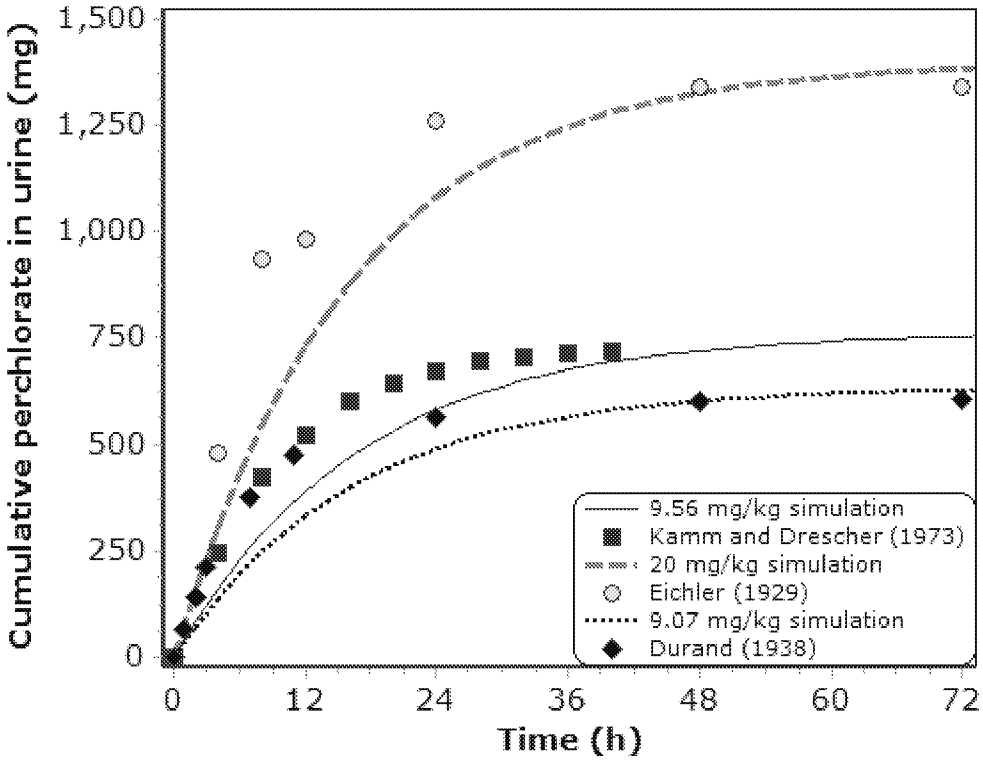
Figure A-49 shows model predictions of cumulative urinary excretion amounts vs. data from Durand (1938), Eichler (1929), and Kamm & Drescher (1973) (one male subject each). The final cumulative excretion for each is matched well, supporting the hypothesis of 100% absorption and urinary excretion on which the model is based. However, the initial rate of excretion (rate of rise in the cumulative amount) is lower than shown by the data. This could be due to inter-individual differences between these 3 male subjects and the female subjects from Greer et al. (2002) used to calibrate the urinary clearance constant and the fact that the model uses the 2.5th percentile of the estimated uncertainty distribution for the median urinary clearance or perchlorate. Better fits are obtained using the 97.5th percentile although that value still yields a prediction slightly slower than observed (results not shown). Also, the doses used in these studies were 20-40 times higher than the highest dose used by Greer et al. (2002). If these doses saturate binding to serum proteins and that saturation is not properly characterized in the model, then the model might not capture a high-dose increase in clearance. Since the error appears to be relatively small and the doses are well above model application, no adjustment to the model parameters was made.

Figure A-49. Predicted cumulative perchlorate in urine vs. data[a]



[a] Data for 1 male subject each are originally from Durand (1938), Eichler (1929), and Kamm & Drescher (1973).

2.2 Thyroid hormone levels and iodine intake in non-pregnant women

In order to evaluate model performance, it is first necessary to identify data and population statistics for model calibration (to represent the range of thyroid hormone levels in the population) and for comparison to model simulations. Data for non-pregnant women from NHANES 2007 to 2012 were restricted using updated criteria based on Hollowell et al. (2002), as described in the memo from Abt Associates, *Analysis Results from Perchlorate Statistical Approach*. The specific inclusion criteria for these data are as follows:

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- Non-pregnant women 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
- Are not taking estrogen, androgen, or lithium supplements
- Do not currently report having a thyroid disease
- Are not currently taking thyroid medication

After applying these selection criteria for women from NHANES studies (2007-2012 data), the resulting thyroid hormone median (2.5^{th}-97.5^{th} percentile) values are:

T4 = 100.3 (T4 = 79.8-142.4) nM,
T3 = 1.74 (1.26-2.55) nM,
TSH = 1.39 (0.45-3.5) mIU/L,
fT4 = 10.3 (7.72*-13.8) pM, and
fT3 = 4.81 (3.99-6.01) pM.

The median (95% CI) TSH level for this population (1.39 mIU/L) is nearly identical to the median reported by Hollowell et al. (2002) for NHANES III (1.38 mIU/L), but they obtained a median (95% CI) for T4 = 111.8 nM (66.9-165.9) nM, about 11% higher than this analysis, based on a sample of 6,182 women, 12 years and older, of mixed ethnicity. Likewise, median (95% CI) T3 reported by Zhang et al. (2016) (1.89, 1.49-2.43 nM) is slightly higher than this analysis. The fT3/T3 from NHANES 2007-12 had a median (95% CI) = 2.82×10^{-3} $(2.06\text{-}3.72) \times 10^{-3}$, very close to results for other studies (see Figure A-37 above, results for non-pregnant women at Gestation week = 0). But fT4/T4 obtained here, 1.00×10^{-4} $(0.71\text{-}1.35) \times 10^{-4}$, is significantly lower than observed by other studies (see Figure A-36 above, results for non-pregnant women at Gestation week = 0).

Since this evaluation of all thyroid hormone levels is based on a data set consistently selected as described above, for a U.S. population, these values from NHANES 2007-12 are used as the appropriate non-pregnant range for dose-response evaluation of the BBDR model.

2.2.1 Estimation of iodine intake

As described in the memo from Abt Associates, *Analysis Results from Perchlorate Statistical Approach*, urinary iodine concentrations from NHANES 2007-12 were corrected using the approach of Pleil & Sobus (2016) to compensate for expected intra-individual variation. The expected geometric mean of iodine urine concentration for an individual (given that the measured urine concentration varies over time, hence from sample to sample) is calculated as:

$$GM_i = \left(\frac{X_i}{GM}\right)^{ICC^y} * GM$$

where: GM_i = predicted geometric mean value for the ith individual

---

* Due to rounding of many reported fT4 values from NHANES to ± 0.1 ng/dL, there is no difference between the 2.5^{th}, 5th, and 10th percentiles for fT4.

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X_i = single spot measurement from the ith individual

ICC = intra-class correlation coefficient, had a value of 0.693 based on the data of (König, Andersson, Hotz, Aeberli, & Zimmermann, 2011)

y = shape factor (in this case we assume y is equal to ½)

GM = geometric mean value for the population (calculated from spot samples).

Estimation of daily urine volume excretion was based on the measured volume and recorded timing of individual samples for NHANES 2009-10 and 2011-12 data. Most participants only gave a single sample, but participants were prompted to submit additional urine samples if their first urine collection was insufficient for testing. A third and final sample was taken if and only if the second was also deemed insufficient.* Therefore, the last urine collection for each participant was deemed the most relevant draw for iodine volumetric rate (and then total iodine excretion) calculation. The urine excretion rate was calculated as the sample volume divided by the time since last urination, then converted to L/d.

For individuals in the 2009-10 and 2011-12 data sets with urine volume data, total iodine intake was first estimated by multiplying the individual estimate or daily urine excretion, as described in the preceding paragraph, by the individual iodine concentration. Summary statistics for the resulting set of iodine ingestion estimates were then calculated. The resulting median iodine intake was 165.2 μg/d, 10th and 90th percentiles = 58.5 and 386.4 μg/d.

Alternately, to make use of the NHANES 2007-08 data for which urine volume was not recorded, the median daily urine volume for 2009-12 data was determined and then this median value applied to all measured urine iodine concentrations (for 2007-12 NHANES data), and statistical summaries determined. The resulting median iodine intake was 170.2 μg/d, 10th and 90th percentiles = 66.9 and 442.6 μg/d. Given the similarity of the two estimates (preceding paragraph vs. this one), but the fact that this second estimate is based on a larger data set, the second set of values are used.

2.2.2 Initial Calibration Sets (Range) for Dose-Response Analysis (U.S. Population)

There is value in using a wide range of observed hormone levels in model evaluation, comparing model predictions to various data sets, in particular to assure that the model reasonably captures overall variability. However, it is not informative to use simulations for individuals at the highest and lowest bound for dose-response analysis, since those individuals can be considered already on the edge of adversity if not past it, leaving no margin of safety. Since the focus of the assessment is for the U.S. population, median, upper and lower bound calibration sets have been estimated from the NHANES 2007-12 data, where the data have been first selected applying the criteria described at the start of this section (2.1).

However, by limiting data to only individuals with thyroid hormone concentrations in the normal range, trends that might occur at very low iodine ingestion levels, for example, might be missed.

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* One measure of insufficiency is if sample volume exceeded 610 ml. While this does not put a strict upper limit on estimated volume/time measured, the largest volume samples have thereby been excluded.

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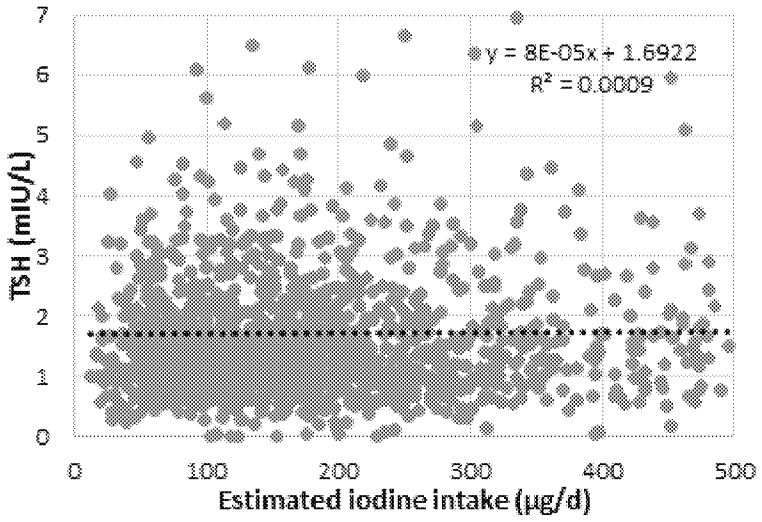
Therefore, a second selection of NHANES 2007-12 data was made, where the only restriction criteria were:

- Non-pregnant women aged 20-44
- Are not taking estrogen, androgen, or lithium supplements
- Do not currently report having a thyroid disease
- Are not currently taking thyroid medication

Figure A-50 and Figure A-51 show TSH, total and free T4, and total and free T3 vs. the estimated iodine ingestion rate from these NHANES data, based on measured urinary iodine, as described just above (**2.2.1 Estimation of iodine intake**). While the maximum estimated iodine intake was estimated to be 21,400 μg/d, only results for 0-500 μg/d iodine are shown to focus on the range of greatest interest. Likewise, a small number of high hormone levels are not shown to better present the majority of the data. However, the trend-line shown in each plot is for all data.

Figure A-50. TSH vs. estimated iodine intake[a]



[a] Data are from NHANES 2007-2012. Individual urinary iodine concentrations are corrected by the method of Pleil & Sobus (2016) then multiplied by the median estimated urine volume per day to obtain estimated individual iodine intake rates. See text for details.

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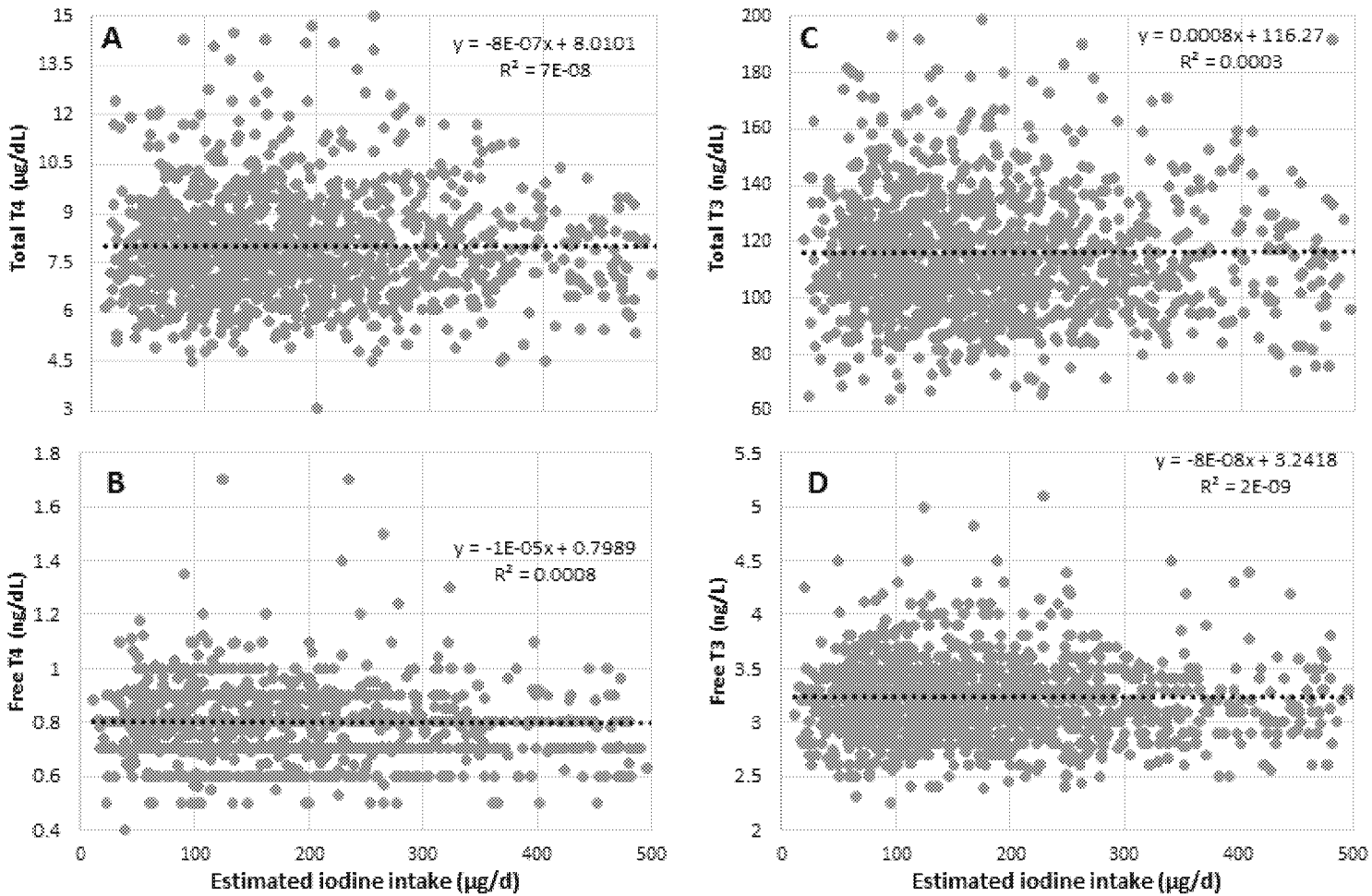
Figure A-51. Total and free T4 and T3 vs. estimated iodine intake[a]



[a] Data are from NHANES 2009-2012. Individual urinary iodine concentrations are corrected by the method of Pleil & Sobus (2016) then multiplied by the median estimated urine volume per day to obtain estimated individual iodine intake rates. See text for details.

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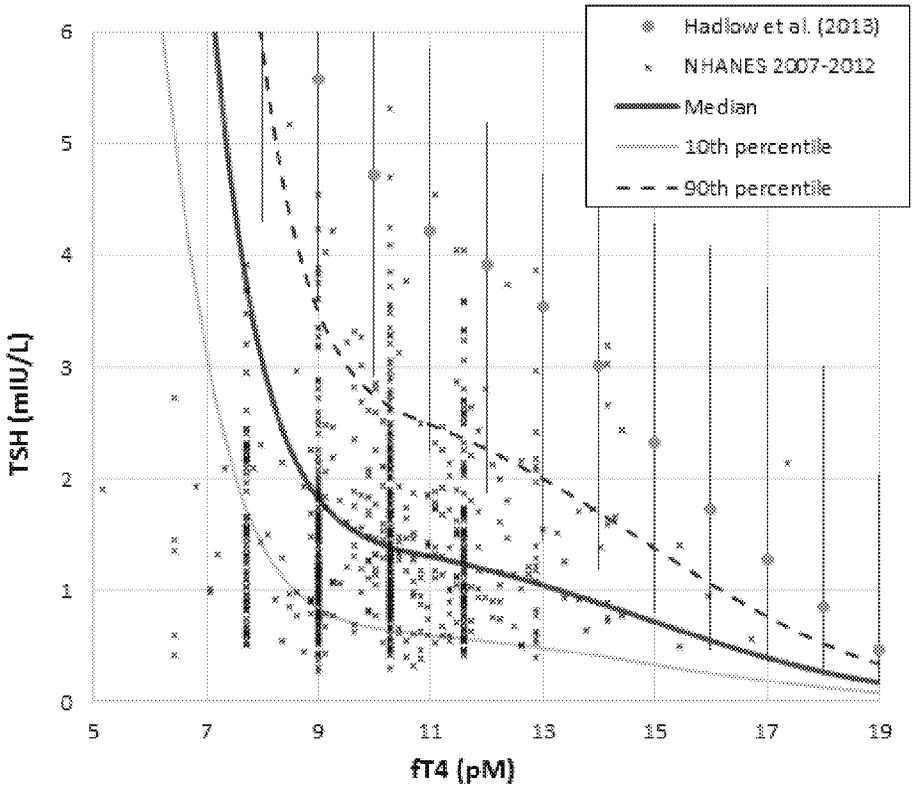
These data seem to indicate that there is almost no change in the population distribution of the TH levels with iodine intake over the evaluated range, except possibly below 75-100 µg/d iodine intake. For example, Figure A-52 compares the correlation between TSH and fT4 from NHANES 2007-12 to that seen by Hadlow et al. (2013). The NHANES data show almost no trend, though the uppermost values appear to increase with decreasing fT4 in a way that parallels the Hadlow data.

Figure A-52. Comparison of the TSH vs. fT4 relationship in Hadlow et al. (2013) and NHANES 2007-12[a]



[a] Curves are adjustments of the empirical function from Hadlow et al. (2013) as described in Section 1.4.13 to the median, 10th and 90th percentiles for TSH and the median fT4 from NHANES 2007-12.

The lack of correlation in NHANES data also contradicts studies such as Anes et al. (2015) which shows a clear, qualitatively expected relationship between T4 and TSH levels in populations from regions with low endemic iodine (low T4 and high TSH) and high endemic areas. If one assumes an average urine excretion rate of 1.45 L/d (median from analysis of NHANES data), then the urine concentrations for the two populations monitored by Anees et al. (2015) correspond to ingestion rates of 93 and 148 µg/d.

A partial explanation for the lack of correlation between iodine intake and hormone levels in NHANES data is the observed relationship between thyroid hormone stores and iodine intake from data collected by Delange (2000), shown in Figure A-53. While the data are relatively sparse, they likewise indicate very little trend in thyroidal stores above 100-150 µg/d, although an approximately linear relationship with iodine intake below that. While the NHANES data (Figure A-50 and Figure A-51) have been corrected for expected intra-individual variation in urine concentration as described by Pleil & Sobus (2016) (Section 2.2.1) the ICC used for the correction may not be sufficient to offset an actual variability in urine concentration. In short, the range in iodine intake estimated from the

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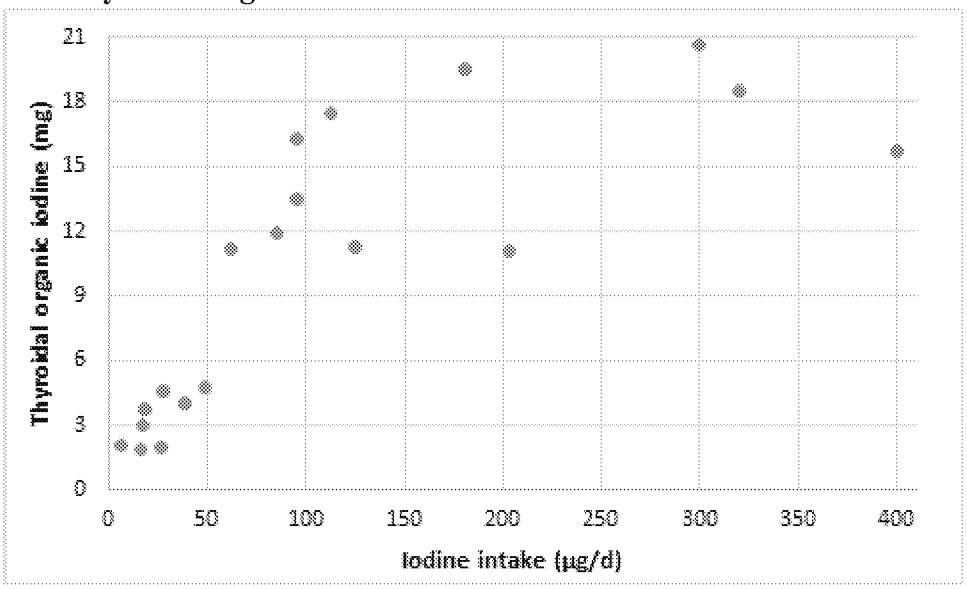
NHANES data may be significantly too wide, with actual iodine intake for most of the population being greater than 100 or 150 μg/d). Data such as Anees et al. (2015) indicate that at only 50 μg/d iodine, for example, fT4 should be significantly decreased and TSH significantly elevated.

Figure A-53. Thyroidal organified iodine stores vs. iodine intake



(Delange, 2000)

Despite this caution, we still seek to use the NHANES data as the most comprehensive observations for the U.S. population. To approximate the population-range of thyroid hormone levels with median, upper, and lower bound calibration sets are defined based on percentiles calculated from the NHANES 2007-12 data set, *with individuals restricted to normal hormone ranges as defined at the start of this section (2.1)*, calculated irrespective of iodine intake. But to readily automate calibration using the script described next, these are associated with a particular iodine intake level, selected to facilitate simultaneous fitting of the model to the thyroid iodine data from Delange (2000). The levels for maximum bound iodide in the thyroid for non-pregnant women (ABNDMAX0 values) are likewise selected to represent the range in the data collected by Delange (2000), although not using a formal calculation of percentiles, given the sparse data.

2.2.3 Computational Script for Thyroid Hormone Calibration and Choice of Calibration Inputs

A computational script was created to calculate the values of specific thyroid hormone kinetic parameters consistent with a given set of thyroid hormone levels, given values of the remaining parameters, for a non-pregnant woman at steady-state. In particular, the thyroid hormone levels (or parameters), "targets" to which the kinetic parameters are fitted are:

- total T4 concentration (CT4TAR);
- total T3 concentration (CT3TAR);
- TSH concentration (TSHTAR); and
- Iodine intake (μg/d) (PDOSEUGD_I), ingestion rate assumed consistent with these targets.

Other parameter inputs varied to match model predictions to the level of bound iodide in the thyroid vs. iodide exposure are:

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- ABNDMAX0, maximum amount of iodide that can be organified or bound in the non-pregnant woman's thyroid;
- Abound_I, the amount organified or bound at PDOSEUGD_I; and
- Afact (no units) = Cfi/(Cbi x Pthy_I), the ratio of free thyroid tissue iodide concentration to the concentration that would be at equilibrium with the thyroid blood, where Cfi is the free thyroid tissue iodide concentration (nM), Cbi is the thyroid blood concentration (nM), and Pthy_I is the tissue:blood equilibrium partition coefficient (no units).

Given these inputs, the script calculates (outputs) the values of:

- KBIND_I, the rate constant for iodide binding in the thyroid;
- KPRODT4F, rate constant for T4 production from the thyroid;
- KPRODT3F, rate constant for T3 production from the thyroid; and
- CLUFT4, the urinary clearance constant for T4.

Given these values, the model for pre-pregnancy conditions yields hormone levels that match that CT4TAR, CT3TAR, and TSHTAR, given PDOSEUGD_I, such that the amount bound in the thyroid at that steady state is Abound_I and Cfi = Afact x Cbi x Pthy_I.

While the calculation can work for any value of most other physiological and biochemical parameters, it was found that this was not possible using values of the metabolic degradation rate constants for T4 or T3, KDEGT4F and KDEGT3F, from Lumen et al. (2013), at modest iodide ingestion rates (e.g., 90-1672μg/d). However, the model could be successfully calibrated in this iodine range if these degradation constants were reduced to 10% of the values used by Lumen et al. (2013). After making this adjustment, the constants were not adjusted further.

Given the lack of correlation between thyroid hormone levels and iodine intake shown by the NHANES data, but the expectation that thyroid iodine levels would decline below 75-100 μg/d, the calibration sets were further refined by using a nominal iodine intake level of 90 μg/d, just below the "knee" in the Delange (2000) data set. In particular, by specifying the thyroidal iodine stores for each of the calibration sets (defined below) at 90 μg/d, it was possible to obtain a range of parameters consistent with the median, 10th, and 90th percentiles of the NHANES data, and the range of thyroidal iodine levels collected by Delange (2000), by adjusting the minimal set of model parameters calculated in the calibration script. Specifically, the calibration assumed that at 90 μg/d iodine intake, and parameter sets as defined below, the corresponding levels of thyroidal iodine stores were 15 (median), 12 (10th percentile), and 17 mg (90th percentile).

The resulting calibration parameter sets are then:

- median calibration set =
  - median values for T4, T3, and TSH;
  - fT4/T4 and fT3/T3 were calculated as the average of those ratios for individuals whose T4 level was within 1% of the median T4;
  - ABNDMAX0 (maximum bound iodide in thyroid) = 17 mg;
  - Abound_i (thyroidal iodide at 90 μg/d iodine intake) = 15 mg;
- 10th percentile calibration set =
  - 10th percentiles of T4 and T3;
  - 90th percentile TSH (given the expectation that TSH increases as fT4 decreases);
  - fT4/T4 = (10th percentile fT4)/(10th percentile T4);

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- fT3/T3 = (10th percentile fT3)/(10th percentile T3);
- ABNDMAX0 = 15 mg; Abound_i = 13 mg; and

➢ 90th percentile calibration set =
- 90th percentiles of T4 and T3;
- 10th percentile TSH (given the expectation that TSH decreases as fT4 increases);
- fT4/T4 = (90th percentile fT4)/(90th percentile T4);
- fT3/T3 = (90th percentile fT3)/(90th percentile T3);
- ABNDMAX0= 19 mg; Abound_i = 17 mg;

In fact, Figure A-50 and Figure A-51 indicate that the combination of hormone levels in any given individual may exist anywhere in the ranges shown; i.e., a low fT4 with a high total T4, and maximal thyroidal stores and actual levels at 90 μg/d iodine intake may also be weakly correlated with iodine intake due to other factors of inter-individual variability. But these combinations are selected to approximate the overall range expected in the population. A more complete variability analysis is conducted later, in which the relationships assumed in this selection are not forced upon the results.

Finally, the rate constant for binding of free iodide in the thyroid, KBIND_I, was found to affect the curvature of the predictions for thyroidal iodine stores vs. iodine ingestion rate at the "knee", while specifically influencing the amount of free iodide in the thyroid. So by varying the assumed value of Afact = Cfi/(Cbi x Pthy_I) at the calibration point to set KBIND_I, the model curvature could be tuned to approximate that shown by the data of Delange (2000) in that region. Since the data are not sufficient to indicate that the curvature varies in any particular way as a function of other thyroid hormone levels, a single value of Afact was set for all three calibration sets, Afact = 10.

2.2.4 Model Simulations in Comparison to Data for Non-Pregnant Women

As discussed above, while the NHANES data selected to identify population ranges for model calibration were restricted to women with hormone levels in the normal range, model predictions should be evaluated for low iodine intake, for which some individuals are expected to have thyroid hormone levels below the normal range and/or TSH above the normal range. Therefore, when showing model predictions vs. data, the second extraction of NHANES 2007-12 was used, allowing for women with abnormal thyroid hormone levels and/or with elevated thyroid antibodies, but not frank thyroid disease. To reiterate, the inclusion criteria for the second set are just:

- Non-pregnant women aged 20-44
- Are not taking estrogen, androgen, or lithium supplements
- Do not currently report having a thyroid disease
- Are not currently taking thyroid medication

The sets of model predictions calibrated as described above are shown in comparison to this more inclusive NHANES data set and (Delange, 2000) data are shown in Figure A-54 and Figure A-55.

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Figure A-54. Model simulations of free and total T3 and T4 levels in non-pregnant women as a function of iodine intake compared to data from NHANES 2007-12

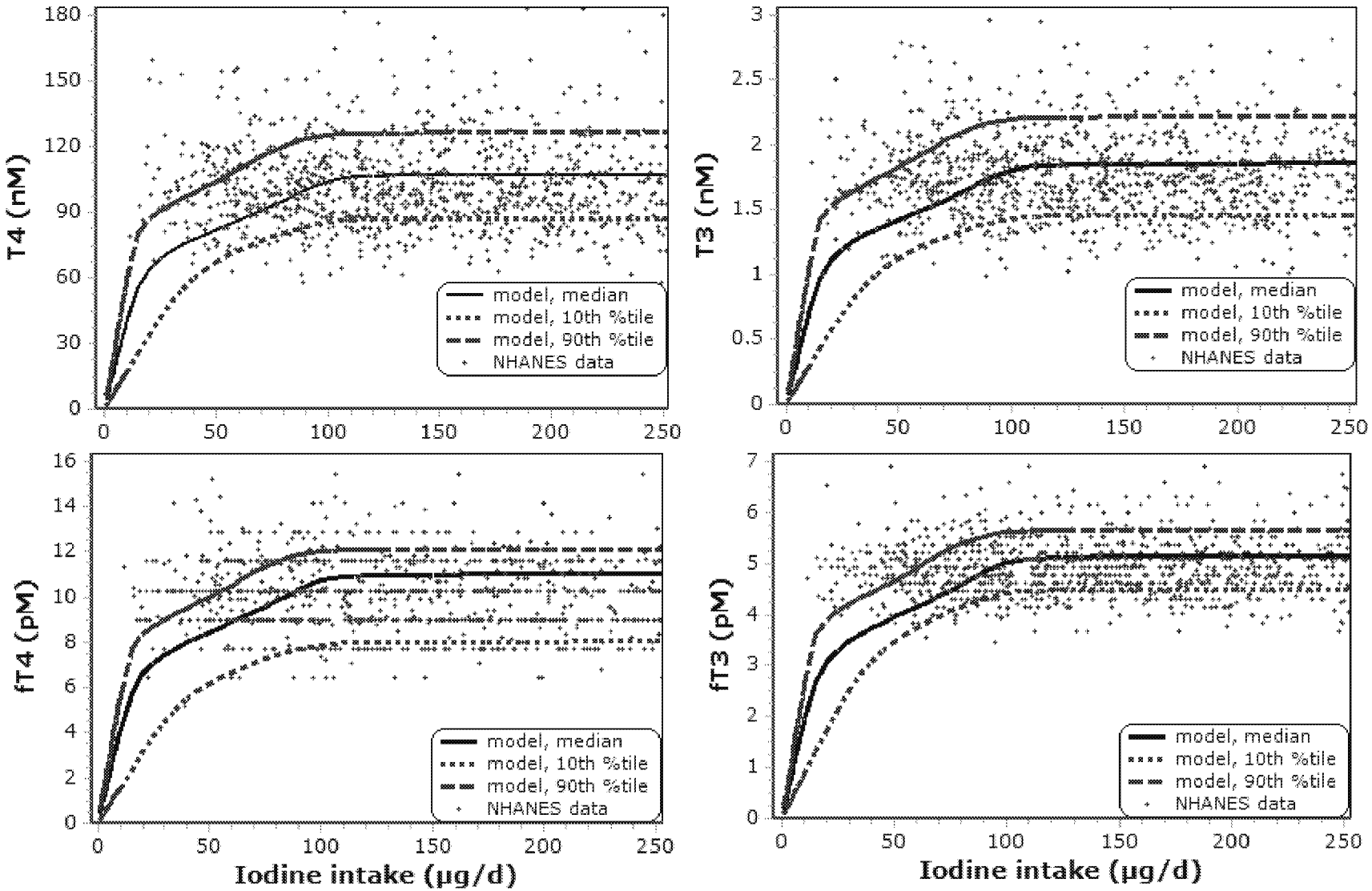

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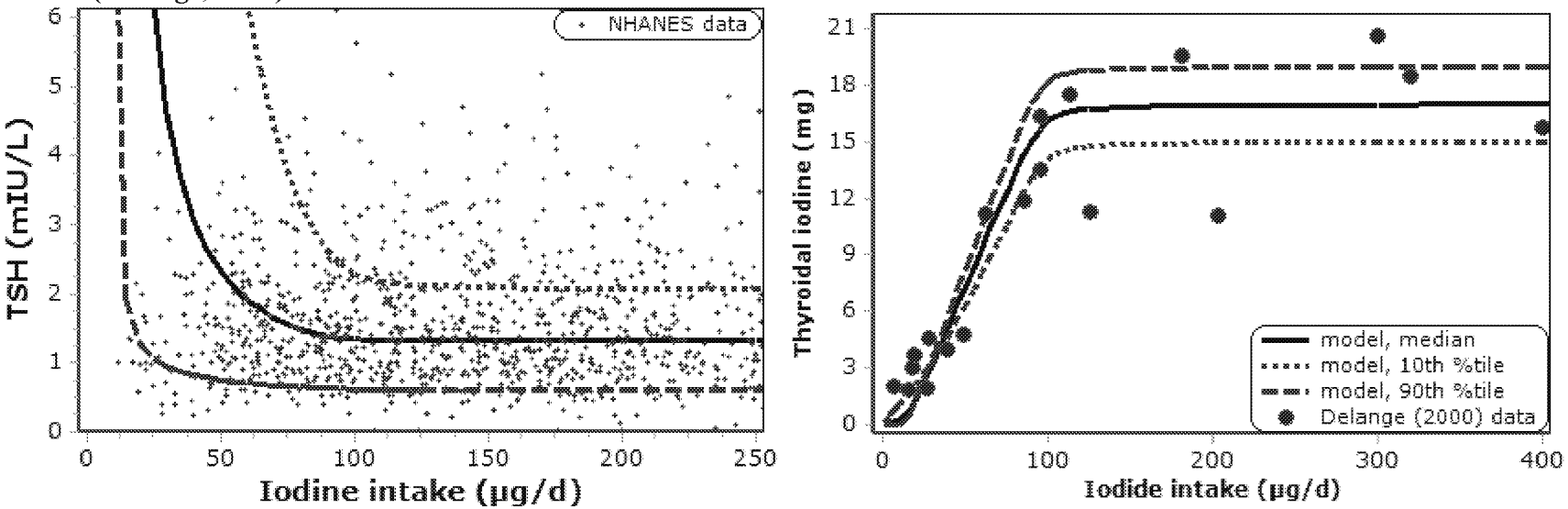
Figure A-55. Model predictions for TSH and thyroidal iodine stores vs. iodine intake compared to data from NHANES 2007-12 and (Delange, 2000)



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The first thing to note about the simulations in Figure A-55 is that the predicted TSH levels (upper left panel) plateau for iodine intake above 100 μg/d. This occurs because given the calibration to match the thyroidal stores data of Delange (2000) (right-hand panel of Figure A-55), the thyroid is already near this maximum at an intake level of 100 μg/d, and even if stores increase 5% above that level, TH production is maintained due to incremental decreases in TSH.

Below 90 μg/d iodine intake, thyroidal stores drop almost linearly with iodine intake, forcing some decrease in thyroid hormone production and circulating concentrations. However, the decrease in TH concentrations is less than proportional, likely as a result of TSH feedback. TSH levels, shown in the left panel of Figure A-55, are predicted to increase dramatically as iodine intake falls and in particular fT4 begins to fall. However, when pREG is reduced (short dash line, model 10th percentile)

For iodine levels between ~ 5 and 25 μg/d a point is reached where iodine availability to the thyroid becomes fully limiting. A factor in this limitation is the rate of plasma flow to the thyroid: it cannot take up iodide faster than it's delivered in the plasma. So TH levels drop precipitously below this point.

The fact that the initial decline in thyroid hormone concentration, between ~30 and 90 μg/d, is not reflected by the data which show little or no decline, may be due to a mechanism not included in the model, such as regulation of thyroid hormone metabolism. If TH metabolic clearance is reduced in response to declining hormone concentrations, then that would cause them to decline more slowly than currently predicted.

Since the effect of perchlorate on the thyroid is roughly equivalent to a reduction in iodide availability, the impact of introducing a mechanism as suggested by this discrepancy would be to reduce the effect of perchlorate predicted by the current model. To put it another way, the current model, which predicts a decline in TH levels between ~30 and 90 μg/d, most likely predicts a stronger perchlorate dose-response for iodine intake in this range than would be the case if additional terms were added to the model so that TH levels drop more slowly.

Finally, model predictions of 24-hour radio-iodide uptake by the thyroid (% in thyroid 24 h after dosing) is shown vs. data collected by Delange (2000) in Figure A-56. Model predictions match the observed data fairly well for iodine intake levels above ~ 50 μg/d, but are less than observed at very low levels. The plateau in the 10th percentile and median simulation curves at the very lowest level reflects the corresponding plateau in the TSH curve seen in Figure A-43, with the stimulation coefficient, pREG, set to 0.4 for the 10th percentile simulation. However, another factor in this model component, demonstrated in the 90th percentile simulation, is that TSH is assumed to stimulate both iodine uptake and thyroid hormone production, which uses thyroidal iodine. Above 50 μg/d iodine intake the rate of iodine turnover in the thyroid is predicted to be much slower than uptake, such that of the radioiodine absorbed in 24 (mostly in the first few hours) very little is excreted. But when uptake and hormone production become extremely high, which occurs for very low intake and pTSH = 3.1 for the 90th percentile simulation, a large fraction of (radio)iodine is excreted in that time, such that the amount remaining at 24 h drops to near zero.

Simulations were also conducted were TSH was assumed to increase iodine uptake to a greater extent than the increase in iodine production. While these simulations yielded radioiodine uptake at low iodine levels closer to the data in Figure A-56, the fit to the total thyroidal iodine vs. intake (right

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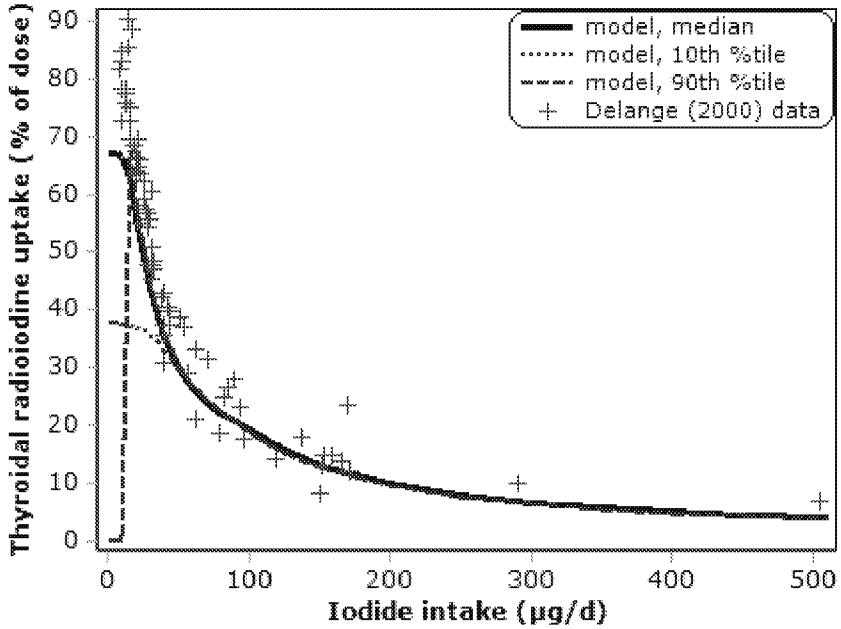
panel of Figure A-55) became worse. In order to have a near-linear increase in thyroidal iodine with intake at low levels, intake and production must be varied in proportion to one another.

Figure A-56. Model predictions for thyroidal 24-h radioiodine uptake vs. iodine intake compared to data from NHANES 2007-12 and Delange (2000)[a]



[a] Considering that the model does not account for physiological changes – growth of the thyroid (goiter) and any accompanying increase in blood flow to it – that would occur at extremely low iodine nutrition, and treats "bound" thyroidal iodine as a single mixed pool, rather than accounting for the sequential processing into thyroidal hormones, the failure of the model at these very low iodine intake levels should not be surprising. The additional model structure development that would be needed to correct the discrepancy is beyond the scope of this exercise. Therefore, it is accepted as indication that the model is not reliable for iodine intake levels below 50 µg/d. While predictions are somewhat low at 50 µg/d, they are still within the range of the data, so predictions at and above this intake level are judged to be acceptable.

2.3 Thyroid Hormone Calibration Sets for Model Evaluation vs. Observed Data During Pregnancy

To facilitate comparison of thyroid hormone parameters across various studies, 2.5th, median, and 97.5th percentile thyroid hormone concentrations from several data sets are collected in Table A-7, below. T4 and TSH values from Hollowell et al. (2002) are included because these are based on analysis of over 6,000 of U.S. women. Results from Zhang et al. (2016) are included because they are for a moderately large sample (n = 301) and because the authors reported results for all parameters of interest. Finally results from La'ulu & Roberts (2011) are used for parameters not reported by Hollowell et al. (2002) because the results are also for U.S. women and they also comprehensively reported values for all parameters, though with fewer subjects (n = 122).

Model predictions using calibrations based on these studies are compared to a larger set of studies after parameter selection is complete. While these three studies may not yield predictions that cover the range for all reported data, they are assumed sufficient for setting parameter ranges for illustrating and evaluating model performance during pregnancy. The calibration sets for U.S. women identified in the previous section from NHANES data alone are used for MCLG application, but by themselves

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may not adequately represent variability among the larger set of populations for which data are available and between laboratories where hormone levels have been measured.

For pregnancy model evaluation, a lower bound set is defined using:

1) the minimum of 2.5th percentile values for T4 and T3, and the maximum of the 97.5th percentile values for TSH from the corresponding triplets in Table A-7;
2) the median value for each parameter in the median column; and
3) the maximum of the T4 and T3 values in the 97.5th percentile column, and the minimum of the 2.5th percentile values for TSH.

This choice assumes that low T4 and T3 values are associated with high TSH values, and vice-versa. For all sets the median fT4/T4 and median fT3/T3 are used, since these are applied to the minimum or maximum values for T4 and T3, respectively as upper/lower bound estimates.

2.3.1 Model Evaluation Results

The upper, middle, and lower curves in Figure A-57, Figure A-58, and Figure A-59 show results given the corresponding 2.5th, median, and 97.5th percentile parameter sets defined in Table A-7, and the other pregnancy-related changes as described above. For each parameter set simulations were run for the three values of the TSH stimulus coefficient, pTSH = 0.398, 1, and 3.09 (see section 1.4.13), resulting in three "triplets" of simulation curves.

The model appears to describe the gestation-related changes reasonably well, and most of the observed variation among various studies and populations. Since the levels at GW = 0 can be tuned to distinct populations or individuals, the "high" and "low" simulation curves for fT4 in Figure A-57 could be adjusted upward to better match the respective data of Li et al. (2014) and Männistö et al. (2011), for example. The current exercise was an attempt to determine if calibration ranges based on only the studies included in Table A-7 would be predictive of all populations. These results show that while that is mostly the case, it is not entirely true. For fT4 (and fT3, Figure A-58), the predicted values which depend on calibrated free/total ratios appear to vary in less predictable ways between studies, hence requiring study- or population-specific values.

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Table A-7. Candidate Initial Thyroid Hormone for Pregnancy Simulations

Thyroid parameter, sources	2.5th percentile	Median	97.5th percentile
T4 (nM) from Hollowell et al. (2002), Zhang et al. (2016), NHANES 2007-2012	66.9, 81.0, 79.8	111.8, 112.4, 100.3	165.9, 149.0, 142.4
fT4 (pM) from La'ulu & Roberts (2011), Zhang et al. (2016), NHANES 2007-2012	10.7, 12.46, 7.72	14.8, 15.76, 10.30	17.7, 19.58, 13.77
resulting fT4/T4 (10^{-4})[a]	1.60, 1.54, 0.97	1.32, 1.40, 1.03	1.07, 1.31, 0.97
T3 (nM) from La'ulu & Roberts (2011), Zhang et al. (2016), NHANES 2007-2012	1.36, 1.49, 1.26	1.89, 1.89, 1.74	3.05, 2.43, 2.55
fT3 (nM) from La'ulu &Roberts (2011), Zhang et al. (2016), NHANES 2007-2012	3.97, 4.09, 3.99	5.24, 4.93, 4.81	6.72, 6.02, 6.01
resulting fT3/T3 (10^{-3})[a]	2.92, 2.74, 3.17	2.77, 2.61, 2.77	2.20, 2.48, 2.36
TSH (mIU/L) from Hollowell et al. (2002), Zhang et al. (2016), NHANES 2007-2012	0.41, 0.78, 0.45	1.37, 2.04, 1.39	4.09, 5.03, 3.49
Iodine intake (µg/d) estimated from NHANES 2007-2012	38.0	170.2	763

[a] Calculated from corresponding values in previous two columns, noting that the 1st value of fT4/T4 is the ratio of the value from La'ulu & Roberts (2011) to that reported by Hollowell et al. (2002).

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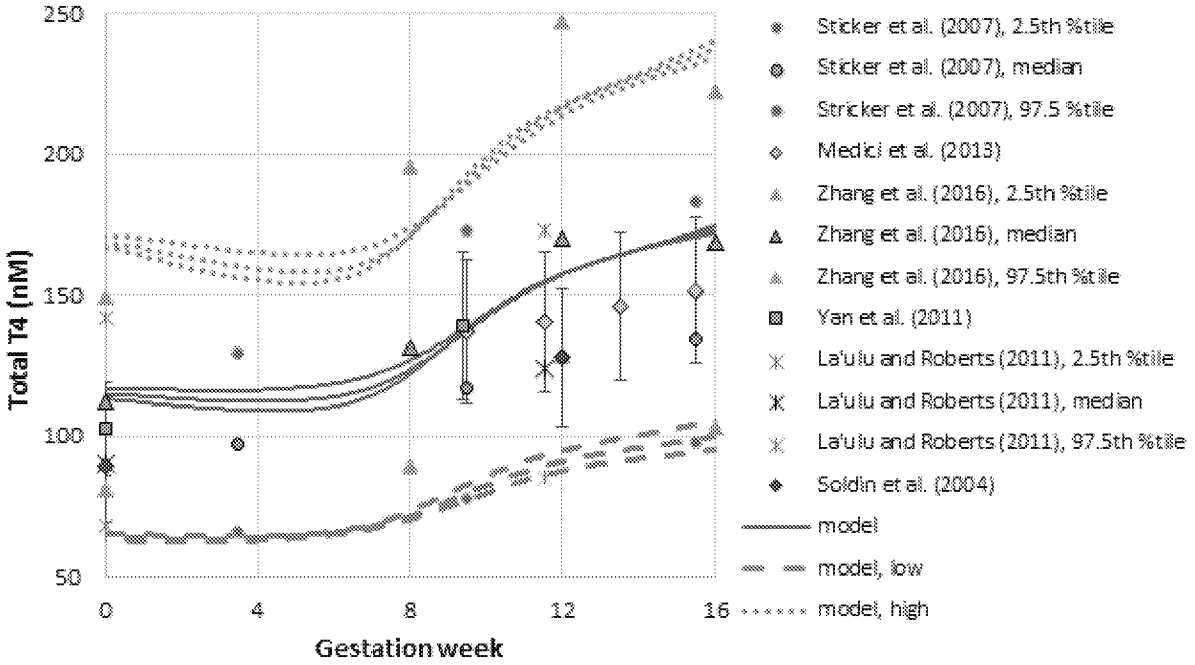
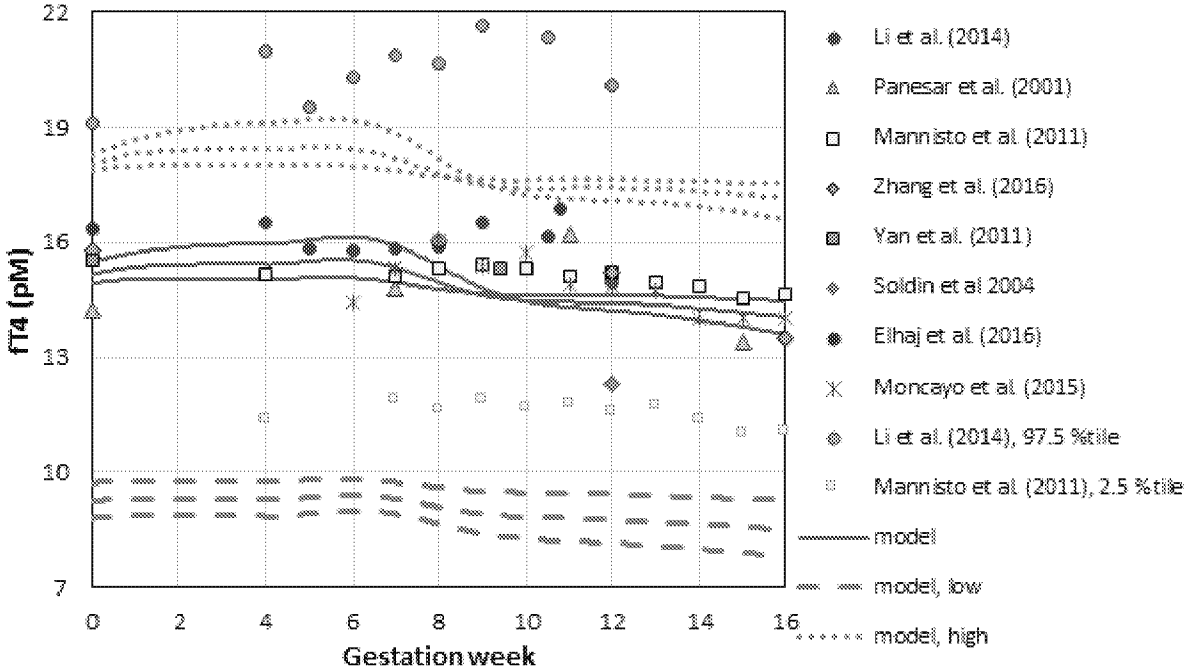
Figure A-57. Total and free T4 during pregnancy vs. gestation week[a]





[a] Data are from Elhaj et al. (2016), La'ulu & Roberts (2011), Li et al. (2014), Männistö et al. (2011), Medici et al. (2012), Moncayo et al. (2015), Panesar et al. (2001), Soldin et al. (2004), Stricker et al. (2007), Yan et al. (2011), and Zhang et al. (2016). Each triplet of model curves are results for varying levels of TSH, as described in Section 1.4.13. Because fT4 decreases in the later part of the first trimester, TSH levels are increasing. The highest-lowest curve in each triplet at GW 16 is for the highest-lowest TSH feedback strength evaluated.

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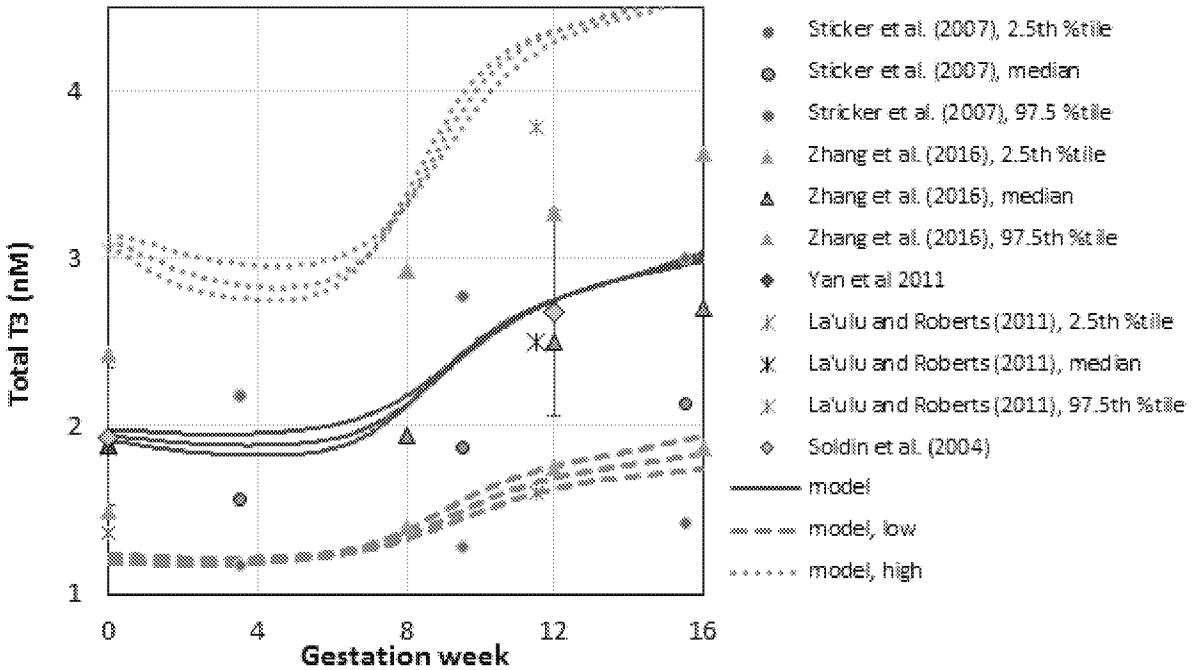
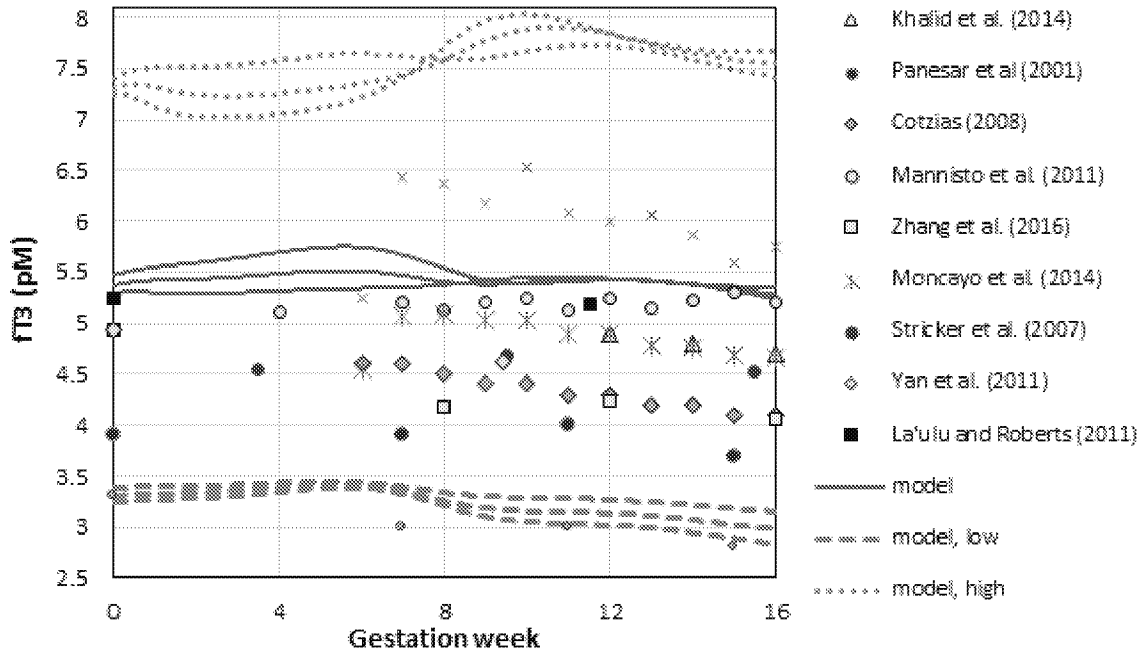
Figure A-58. Total and free T3 during pregnancy vs. gestation week[a]





[a] Data are from Cotzias et al. (2008), Khalid et al. (2014), La'ulu & Roberts (2011), Männistö et al. (2011), Moncayo et al. (2015), Panesar et al. (2001), Soldin et al. (2004), Stricker et al. (2007), Yan et al. (2011), and Zhang et al. (2016). See Figure A-57 legend for other details.

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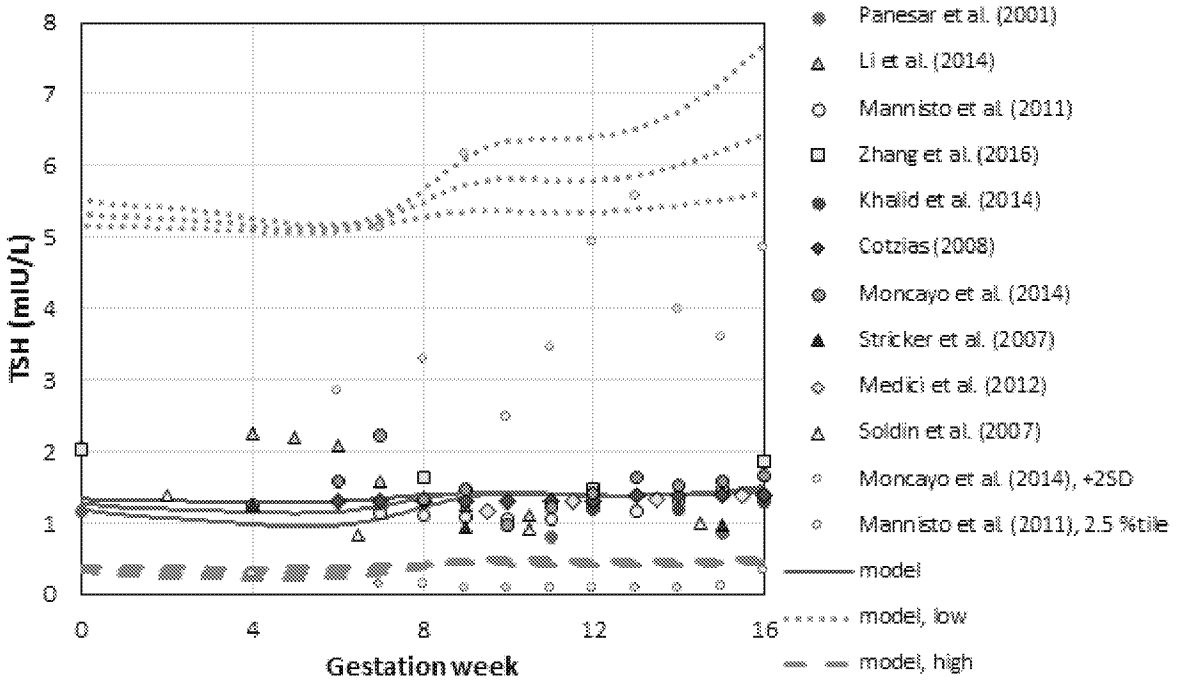
Figure A-59. TSH during pregnancy vs. gestation week[a]



[a] Data are from Cotzias et al. (2008), Khalid et al. (2014), Li et al. (2014), Männistö et al. (2011), Medici et al. (2012), Moncayo et al. (2015), Panesar et al. (2001), Soldin et al. (2007), Stricker et al. (2007), and Zhang et al. (2016). Because TSH is assumed to be inversely related to fT4 levels, the "model, high" calibration pairs upper percentile fT4 (and other thyroid hormone levels) with lower percentile TSH levels, and vice-versa. Because fT4 decreases in the later part of the first trimester, TSH levels are increasing. But the highest curve in each triplet at GW 16 is for the lowest TSH feedback strength evaluated and vice-versa, because when TSH stimulation strength is increased, there is a larger impact on fT4, so fT4 is maintained at a higher level than occurs with lower TSH feedback, with the result that there is a lower total increase in TSH.

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3. Sensitivity Analysis

3.1 Local Sensitivity Analysis

A local sensitivity analysis was conducted to provide a measure of the influence of model parameters on a measure of perchlorate dose-response. In particular, the decrease in fT4 plasma concentration ("CFT4") between zero perchlorate exposure and exposure to 4 μg/kg/d, is used as the response; i.e.,

$$y(p, GW) = CFT4(p, GW, 0) - CFT4(p, GW, 4),$$

where p is the parameter value, GW is gestation week evaluated, and '0' or '4' represent the perchlorate dose. The sensitivity of y(p, GW) was evaluated at GW = -1 (pre-pregnancy), 12, and 16.

The fact that the decrement in CFT4 is used as a measure of response means that if a parameter changes *both* CFT4(p, GW, 0) *and* CFT4(p, GW, 4) to the same extent, it is considered to have no influence: the parameter may affect predicted CFT4, but it doesn't impact our evaluation of the dose-response for perchlorate. Determining whether a particular parameter impacts CFT4 in control individuals is important for understanding the underlying factors of inter-individual variability. But for this analysis the concern is on the predicted dose-response, and when the control prediction is changed, that is equivalent to evaluating a different individual in the population.

If parameter p is varied between $p^+ = 1.01*p$ and $p^- = 0.99*p$, then a local, normalized sensitivity coefficient can be computed as:

$$SC(p) = \frac{y(p^+)-y(p^-)}{y(p)} \cdot \frac{p}{p^+-p^-} = \frac{y(p^+)-y(p^-)}{y(p)} \cdot 50.$$

SCs were calculated for both a median and a 10th percentile individual, who respectively have median (pTSH = 1) and low (pTSH = 0.4) TSH signaling strength. In both cases, iodide intake rates of 50 μg/d were assumed to maximize the effect of perchlorate in the range for which the model is considered valid. Local sensitivity coefficients for all biochemical and physiological parameters were evaluated, while parameters that specify dose, dose timing, and initial conditions were not. Results are provided in Table A-8. For the sake of brevity, only parameters with an absolute SC ≥ 0.1 for at least one time-point/calibration are listed. In several cases where sensitivity coefficients were identical in absolute vale, they are listed together.

The set of parameters identified as significantly influential (have an SC ≥0.1) is understandable, given that results are determined at or near steady state. For example, binding of perchlorate to serum proteins and sequestration in red blood cells would impact the rate of change after an exposure event, but not the long-term average blood concentration, so the response of interest is not sensitive to the related parameters.

3.1.1 Sensitivity to Physiological Parameters

Four physiological parameters are identified as significantly influential: **BW0** (initial BW), **VDFT40** (initial volume of distribution for T4), **QFC0** (initial cardiac output), and **QFTHY0** (initial fraction of blood flow to the thyroid). All of these initial values are multiplied by adjusting equations for pregnancy related changes, so they have an impact in both phases. Since total thyroid blood flow is determined by **QFC0*QFTHY0**, these both represent the impact of delivery to the thyroid. The fact

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that the sensitivity coefficient for these parameters is higher for the median individual likely reflects a greater utilization of available iodide by such an individual to maintain her higher level of fT4.

Table A-8. Significant Local Sensitivity Coefficients

Parameter	Median individual, pTSH = 1			10th percentile individual, pTSH = 0.4		
	GW -1	GW 12	GW 16	GW -1	GW 12	GW 16
BW0	-0.90	-0.71	-0.64	0.57	0.66	0.70
VDFT40	-0.28	-0.36	-0.30	0.09	0.18	0.18
QFC0, QFTHY0	0.16	0.14	0.12	0.02	0.00	0.00
VMAXNISF_THY_I (-KMNIS_I)	0.65	0.53	0.47	-0.37	-0.41	-0.42
KMNIS_P	-0.96	-0.96	-0.96	-0.98	-0.98	-0.98
KDEGT4F	-0.28	-0.22	-0.24	0.09	0.10	0.13
CLFUI	-0.82	-0.67	-0.60	0.36	0.41	0.43
CLFUP	-0.95	-0.96	-0.96	-0.98	-0.98	-0.98
CLUFT4	-0.91	-0.63	-0.59	0.22	0.20	0.22
FRT40	1.94	1.58	1.42	-1.14	-1.30	-1.32
AOBT4	0.00	-0.14	-0.24	0.00	0.07	0.12
PTSHV	-0.38	-0.38	-0.41	-0.72	-0.69	-0.67
KHCG	0.00	0.13	0.08	0.00	-0.08	-0.06
CT4TAR	0.75	0.60	0.53	-0.84	-0.92	-0.93

[a] Normalized sensitivity coefficients for the effect of the parameter on perchlorate dose-response. A positive value means that increasing the parameter increases the relative change in fT4 concentration vs. perchlorate exposure and vice-versa. See text for additional details.

BW0 and **VDFT40:** The total volume of distribution for T4 is determined by **BW0*VDFT40**, so the similar pattern in the SCs for **BW0** and **VDFT40** reflects this co-dependence. In particular, some of the effect of BW0 is because of its impact on T4 volume of distribution. However, the fact that the SCs for both of these go from negative for the median individual (with pTSH = 1) to positive for the 10th percentile individual (with pTSH = 0.4) is harder to understand. The Vmax for NIS uptake scales as $BW^{0.75}$, which means that if BW increases by 10%, for example, VMAXNISF_THY_I only increases by 7.4%. Moreover, iodine intake is fixed, not scaled with BW, while perchlorate dose is scaled with respect to BW, which means that perchlorate levels remain similar while iodide and thyroid hormones are distributed into a larger volume of distribution when BW increases. The fact that perchlorate potency increases with BW for the 10th percentile individual with pTSH = 0.4 is understandable from that standpoint.

However, the TSH response curve is highly nonlinear (see Figure A-55) and increasing BW would shift an individual onto a steeper part of the curve. For an individual with stronger TSH stimulation (pTSH = 1), this could make that person more resilient to further decrements in iodine, offsetting the impact on the baseline Vmax and volume of distribution.

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3.1.2 Sensitivity to Biochemical Parameters

The sensitivity to **KMNIS_P** is uniformly strong and negative, since a higher level is equivalent to weaker affinity of perchlorate for the NIS, and the sensitivity to urinary perchlorate clearance (**CLFUP**) is uniformly strong and negative because clearance reduces the perchlorate in the blood. Likewise, the sensitivity to the TSH stimulation strength (**PTSHV**) is uniformly strong and negative since increases in this parameter increase the individual's resiliency to reduced iodide availability.

For **VMAXNISF_THY_I**, an increase in the value for a median individual means that less iodine is left in circulation and the impact of inhibiting that step could then become stronger, hence the positive SCs. But it is then not clear why increasing this Vmax would make the 10th percentile woman *less* sensitive to perchlorate, since the same factors apply and that woman is assumed to have lower TSH stimulation strength. Since the rate of iodine uptake is proportional to the ratio, **VMAXNISF_THY_I / KMNIS_I**, it follows that the SCs for **KMNIS_I** are equal in magnitude but the negative of **VMAXNISF_THY_I**.

That increasing **CLFUI** makes the 10th percentile woman more sensitive is understandable because this change reduces iodide available to the thyroid, and this individual does have pTSH = 0.4. The negative effect of this parameter on the median individual may reflect the shift to a steeper portion of the TSH feedback curve, when pTSH = 1.

Both urinary clearance of T4 (**CLUFT4**) and metabolic degradation of T4 (**KDEGT4F**) have the effect of reducing the amount of available T4, so it is expected that they should have the same pattern. Since degradation leads to recycling of the iodide, its effect is weaker than clearance. Since an increase in **CLUFT4** also removes iodine from the system, it also has a similar pattern to urinary clearance of iodine (**CLFUI**). Again it appears that when pTSH stimulation is stronger, that more than offsets the impact of reducing the amount of T4 available.

Increasing the fraction of free T4, **FRT40**, increases the rate of its urinary clearance while simultaneously moving the individual onto a less steep portion of the TSH stimulation curve, which can explain why increasing it makes the median individual more sensitive to perchlorate. The pattern for **FRT40** is the same as the pattern for **VMAXNISF_THY_I**, so there is again uncertainty as to why the SC becomes negative for the 10th percentile individual. Since **FRT40** is determined from the population percentile being modeled, the range of its possible values and impacts implies a range of sensitivity to perchlorate in the population.

AOBT4 is a parameter that effects the free T4/total T4 ratio during pregnancy, which is a function of GW. An increase in AOBT4 leads to a decrease in the ratio, hence the pattern for this parameter is the opposite of **FRT40**. Since the change during pregnancy is modest (see Figure A-57), the impact is not strong

KHCG determines the response of T4 and T3 production to hCG, hence informs sensitivity both to this parameter directly and the empirically fitted curve for hCG. Since hCG peaks around GW 12, the effect is strongest at that time-point. The pattern is otherwise like that of **FRT40**.

Finally, **CT4TAR** shifts the calibration of the TSH response curve. The changing sign is likely due to the difference in strength of TSH stimulation between the two scenarios. Since it is the T4 level used to calibrate the model for the population (i.e., median vs. 10th percentile), but the sensitivity analysis is conducted without re-calibration for each parameter increment, these SCs can best be

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interpreted as pointing to the importance and strong nonlinearity in this part of the model, which depends on the assumed level of pTSH.

3.2 Comparison to 3rd Trimester Model

Sensitivity of model predictions to the physiological differences between the 1st and 3rd trimester of pregnancy can be evaluated by comparing model predictions of perchlorate's effects with the 1T BBDR model to the model of Lumen et al. (2013), which describes iodine nutrition, thyroid hormone status, and the dose-response for perchlorate in the late-gestation (near-term) mother and fetus (this is subsequently referred to as the 3T BBDR model). Since the 3T model includes explicit compartments for the near-term placenta and fetus, this comparison includes the extent to which those compartments impact maternal iodide and thyroid hormones.

However, the 3T model does not include TSH feedback. Therefore, to evaluate the extent to which changes in physiology that the 3T model does include impact model predictions, the comparison includes results for the 1T model with TSH feedback strength set to zero.

A number of other structural and parameter value differences also distinguish the maternal 3T model from the 1T model. To be clear, these are components of the model which relate to maternal iodine and TH kinetics, independent of how other physiological changes and explicit placenta and fetus sub-models. So to further inform the comparison of the two models, in particular to show how much difference the placenta and fetus make vs. details of the maternal model, a revision of the 3T model was created such that these maternal features match or are set consistently with the 1T model. For example, urinary clearance accounts for the difference between the end of pregnancy and non-pregnant women in the same way that was done for the 1st trimester. The specific revisions follow.

A feature of the Lumen et al. (2013) model which makes direct comparison problematic is that the saturation of iodide storage in the thyroid is achieved in that model by varying the urinary clearance constant for iodide as a function of iodine intake, rather than using an explicit term for maximal binding of iodide in the maternal thyroid, which is incorporated into the 1T model. (The fetal thyroid model in the 3T model does have the limitation due to a maximal binding capacity.) While this variation in urinary clearance works empirically, there is no known physiological mechanism for regulation of iodine clearance, and if such a mechanism existed it would have to depend on systemic levels of iodide or TH levels, not the rate of ingestion. Therefore, urinary clearance in the revised 3T model was made independent of iodide levels, as is done in the 1T model, and the maximal binding term added to the maternal thyroid.

In addition to this change in model equations, the parameters for perchlorate and iodide clearance were set consistent with 1T model; i.e., by extrapolating from the results of the re-analysis of Greer et al. (2002) provided in Section 1.3.5, using the gestation-age curves described in Section 1.4.8. Specifically, at GW = 40 iodine urinary clearance is predicted to be 1.892 times the value for the non-pregnant woman, or 0.1253 $L/(h*kg^{0.75})$ and perchlorate urinary clearance is predicted to be 1.36 times the value for the non-pregnant woman, or 0.1428 $L/(h*kg^{0.75})$.

Similar to iodine clearance, degradation of T3 was described as a function of iodine ingestion in the Lumen et al. (2013) model. While T3 metabolism may be regulated by hormone levels, it would not be directly responsive to iodine intake, so the T3 degradation was set as a fixed constant. Results are presented for both 100 and 50 μg/d iodide to allow for comparison at a level where thyroid binding is partly saturated with a lower level where it is not. Scaled constants for the degradation of T3 and T4,

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and urinary clearance of T4, were matched to the 1T model, but the values used in the computation are scaled by $BW^{0.75}$, so the pregnancy-related change in maternal BW to the 3rd trimester is still included.

For the median individual in the 1T model, the maximum amount of iodide bound in the thyroid was 17 mg and the binary binding constant in the thyroid is KBIND_I = 0.00312 h^{-1} $nmol^{-1}$, hence these values were used in the revised 3T model. In order for the model to describe thyroid saturation in the appropriate range of iodine intake, the production constants for T4 and T3 from the 1T model were also used.

Finally, the affinity constant for perchlorate is also set to the value used for the 1T BBDR model, from Section 1.3.5, 488.7 nM (the 2.5th percentile of the distribution estimated for the median of KMNIS_P).

Results for the 1T BBDR model, with and without TSH feedback, for the median individual at GW 12 and 16, were compared to results for the original and revised 3T model in Table A-9. The parameter, pTSH, determines the strength of TSH feedback: pTSH = 1 can be considered full feedback, pTSH = 0 is no feedback, and pTSH = 0.4 is the approximate lower bound estimated from NHANES data, and can be considered weak feedback.

The 3T model was previously determined to be unreliable for predictions below 100 μg/d iodine intake because predicted fT4 levels then fall below the euthyroid range for which the model was calibrated and the model does not account for TSH regulation. However, in order to see how the revisions described above impact model predictions in comparison to the effect of TSH feedback, which is much stronger at 50 μg/d, 3T model predictions (with and without revision) are also provided at that low iodine intake.

The results in Table A-9 show that the effect of TSH regulation in the 1T model at 100 μg/d iodine intake is to reduce the perchlorate dose-response by approximately 25-50%, depending on GW. At 50 μg/d iodine, the absolute response (difference between control and exposed) is reduced by about 2/3. Not surprisingly, weak TSH feedback (pTSH = 0.4) results in a change from control that is intermediate between that of no (pTSH = 0) and full (pTSH = 1) regulation. Because the TSH regulation strength also effects the predicted TSH level in the absence of perchlorate, the absolute fT4 variation is more complex, so it is more useful to focus on the difference from control.

Using full TSH regulation (pTSH = 1), the 1T model is about an order of magnitude less sensitive than the model as published by Lumen et al. (2013) (3T model, unchanged). However, much of this difference is not due to the TSH regulation, but due to other differences in the model structure and parameters, which were introduced to increase the biological realism in the 1T model and to more accurately calibrate it to existing data, particularly at 100 μg/d iodine intake. When similar changes are applied to the 3T model ("Revised") the resulting dose-response is similar to the 1T model without TSH regulation at 100 μg/d iodine intake, and are 5-6 times weaker than the unchanged 3T model. The revised 3T predicted dose-response is about 75% stronger than the 1T model without TSH feedback at 50 μg/d iodine intake.

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Table A-9. Comparison of 1st Trimester and 3rd Trimester Model Predictions at 100 and 50 µg/d Iodine Intake

free T4 (control – value)		1T Model (GW 12)			3T Model (GW 40)	
Iodine (µg/d)	Perchlorate (µg/kg/day)	pTSH = 1	pTSH = 0.4	pTSH = 0	Unchanged	Revised
100	0	10.19	10.20	10.32	11.77	10.70
	2	10.14 (0.05)	10.13 (0.07)	10.21 (0.11)	11.15 (0.62)	10.58 (0.12)
	4	10.09 (0.10)	10.05 (0.15)	10.10 (0.22)	10.60 (1.17)	10.49 (0.21)
50	0	8.28	7.49	5.50	8.40	9.25
	2	8.25 (0.03)	7.44 (0.05)	5.39 (0.11)	7.98 (0.42)	9.07 (0.18)
	4	8.21 (0.07)	7.39 (0.10)	5.29 (0.21)	7.61 (0.80)	8.90 (0.35)

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4. Approximate Uncertainty and Variability Analysis of Key Parameters

A semi-quantitative analysis of the uncertainty and variability of the parameters identified in the Local Sensitivity Analysis (LSA) follows. The local sensitivity of *all* model parameters was evaluated for the LSA, but only parameters with a sensitivity coefficient (SC) whose absolute value is greater than 0.1 for at least one time-point/population percentile were listed in Table A-8 (i.e., the SCs for other parameters were evaluated but not shown since $|SC| < 0.1$). This uncertainty/variability (U/V) analysis addresses that subset of model parameters.

The objective of the U/V analysis is to estimate the degree of variability and uncertainty in key parameters and the potential magnitude of their impact on model predictions. However, except for the parameters addressed by the Bayesian analysis of Greer et al. (2002) data, statistically rigorous uncertainty ranges have not been defined for the parameters. In several cases, representative upper and lower values were obtained during parameter estimation; e.g., by fitting an empirical curve for pregnancy-related changes to the highest or lowest data set. These ranges were not defined in a statistically rigorous manner. For other parameters or curves, such as BW increase with pregnancy, a precise range was not obtained. Nevertheless, it is possible to obtain a rough estimate of the range compared to the central estimate by considering the range of the data, and the number of data sets supporting a specific parameters or empirical curves. This approach seeks to identify the maximal impact of uncertainty or variability in any given parameter on model predictions, when varied one at a time.

By multiplying the estimated variability or uncertainty by the average or maximum absolute sensitivity coefficient (SC) obtained in the LSA, a semi-quantitative measure of the overall impact of the variability or uncertainty can be estimated. This approach is similar to the analysis of Sweeney, Gargas, Strother & Kedderis (2003) who estimated the coefficient of variation for a model output using the sum of ($SC_j^2 x CV_j$), where SC_j is the SC for parameter "j" and CV_j is its coefficient of variation. Here the product of SC_i and a measure of variability or uncertainty provides an approximate measure of the contribution of parameter "j" to the overall uncertainty in the model prediction. For example, a parameter whose SC is 0.2 has the potential to impact model predictions. But if the data indicate that the uncertainty is ± 50% of the mean value, which may seem large, the impact of that uncertainty is only expected to be ± 10% of the mean model output (50% x 0.2).

For some parameters such as maternal BW, the uncertainty for any given individual is quite small. BW can be easily measured accurately. But there is inherent population variability that cannot be reduced by collection of additional data. For those parameters that significantly impact the perchlorate dose-response and that are inherently variable, one must then conclude that there is resulting variability in the sensitivity of individuals in the population to perchlorate.

Table A-10 summarizes the findings of this uncertainty and variability evaluation. The sensitivity column provides the range (and an average) of absolute SCs from the preceding LSA. The "parameter variability" column provides a relative range, for example (U – L)/(2*median), where "U" is an upper bound or confidence limit and "L" is a lower bound or limit, or 2 times the coefficient of variation (2*CV), for the *variability* in parameters for which such estimates are possible and where the parameter range or variance is reasonably attributed to inter-individual variability. (The estimation of variability for each parameter is described in detail in the text following Table A-10.) The impact of

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variability, listed in the "potential impact" column, is estimated by multiplying the parameter variability by the *maximum* absolute sensitivity, since this incorporates variability in iodine intake and gestation week evaluated. Parameter *uncertainty* is similarly calculated, where possible, and the resulting relative range can be reasonably attributed to uncertainty (lack of information or imprecision) that might be reduced through further collection of data. (The estimation of uncertainty for each parameter is described in detail in the text following Table A-10.) The impact of uncertainty was calculated using the average absolute sensitivity (times the parameter uncertainty), as a measure of average impact. A parameter may have wide variability in the population, and this is not a matter of imperfect knowledge, and that variability may result in inter-individual variability in sensitivity to perchlorate.

Table A-10. Uncertainty and Variability Summary with Potential Impact on Dose-Response

Parameters with maximum |SC| > 0.1 (Table A-8)	Absolute SC (Table A-8) *	Variability		Uncertainty	
		Parameter variability	Potential impact	Parameter uncertainty	Potential impact
KMNIS_P‡	0.96-0.98 (0.97)	~ 0	~ 0	0.86	**0.8**
CLFUP‡	0.95-0.98 (0.97)	0.82	**0.8**	0.16	0.2
FRT40	1.14-1.94 (1.45)	0.34	**0.7**	0.2	0.3
CT4TAR	0.6-0.93 (0.76)	0.26	0.2	~ 0	< 0.1
PTSHV, PTSHK‡†	0.38-0.72 (0.54)	1.35	**1**	1.35	**0.7**
CLFUI	0.36-0.82 (0.55)	0.82	**0.7**	0.2	0.1
VMAXNISF_THY_I (-KMNIS_I)	0.37-0.65 (0.48)	0.4 (~ 0)	0.3 (~ 0)	0.27 (~ 0)	0.1 (~ 0)
CLUFT4	0.2-0.91 (0.46)	0.41	0.4	~ 0	~ 0
KDEGT4F†	0.09-0.28 (0.18)	0.52	0.1	0.52	< 0.1
BW0	0.57-0.9 (0.7)	0.4	0.4	~ 0	~ 0
VDFT40	0.09-0.36 (0.23)	0.28	0.1	0.5	0.1
AOBT4	0-0.24 (0.1)	0.25	< 0.1	0.25	< 0.1
QFC0, QFTHY0	0-0.16 (0.07)	0.4	< 0.1	0.2	< 0.1
KHCG	0-0.13 (0.06)	0.85	0.1	0.26	< 0.1

* Values are range of absolute sensitivity coefficients (SCs) across iodine intake and gestation times evaluated (numerical average of absolute sensitivities)

‡ Lower bound estimates of KMNIS_P and CLFUP (5th percentile of the estimated distribution for the median) and of PTSHV and PTSHK (approximate lower bound = 0.4), which result in higher sensitivity to perchlorate than median estimates, were evaluated and used to derive the MCLG. The likelihood that KMNIS_P or CLFUP are significantly less than the 5th percentiles used is considered low. Likewise, the likelihood that PTSHV and PTSHK are less than 0.4 is considered low. Hence the remaining uncertainty is qualified as low.

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[†]For PTSHV, PTSHK, and KDEGT4F one cannot distinguish variability and uncertainty due to lack of data. The potential impact is calculated for both, but the combined uncertainty and variability would likely be less than obtained by adding these estimates.

The discussion below generally addresses the parameters in order of sensitivity from highest (average) to lowest, but parameters are also grouped according to the model component that they impact.

4.1 KMNIS_P, CLFUP, KMNIS_I, VMAXNISF_THY_I, and CLFUI

With the exception of KMNIS_I, this set of pharmacokinetic parameters are those analyzed in Section 1.3 of Appendix A. This was a rigorous statistical analysis making use of the data from the well-defined, clinical study of Greer et al. (2002). While Greer et al. (2002) provide data of a quality and value not often available for toxic chemicals and measures the effect of perchlorate on the key precursor effect, iodide uptake inhibition, the number of female subjects is limited: only 4 per dose group. Even if data from both male and female subjects were used, the total number (8 per dose group) would be inadequate to characterize *variability* in the U.S. population. But other data sources can be used to evaluate variability in urinary clearance (**CLFUP** and **CLFUI**) and iodine uptake (**VMAXNISF_THY_I**).

The enzyme affinity parameters, **KMNIS_P** and **KMNIS_I**, are intrinsic properties of the NIS, for which there is no known polymorphism (the molecular structure does not vary in the population), and the iodide and perchlorate anions. Therefore, no inter-individual variability is expected for these parameters in the general population, and so entries of "~0" have been entered in the "variability" columns corresponding to these parameters. The estimated *uncertainty* in the value from the Greer et al. (2002) data should adequately represent the overall uncertainty in the parameter (i.e., should not underestimate the uncertainty). Only the top 3 dose groups showed a significant effect on iodide uptake, hence informing **KMNIS_P**, and because of the presumed induction of NIS in the top group, data from only the middle two groups, were combined to estimate that parameter and the range of estimated population median values (Table A-5 and Table A-6). In particular, the 2.5th sampling percentile for the median from the six subjects with reasonably consistent values (set A2, "KM_TPNG" in Table A-6) was selected for use. Therefore, the uncertainty is characterized as (97.5th – 2.5th)/(2*50th) percentiles from that sample: 0.86. If 0.86 is multiplied by the average SC from Table A-8 (0.97) the result, rounded to one significant figure, is 0.8. (All uncertainty and variability impacts described below and listed in Table A-10 are likewise rounded to one significant figure.)

The uncertainty impacts for **CLFUP** and **CLFUI** based on results in Table A-5 ("CLUC_P" and "CLUC_I") are only 0.2 and 0.1, respectively. But the range of iodide clearance reported by Aboul-Khair et al. (1964) indicating inter-individual variation, which is presumed to also apply to perchlorate, is a coefficient of variation (CV) of 41% among 13 non-pregnant control subjects, leading to a parameter variability of 2*CV = 2*0.41 = 0.82.

The uncertainty for the estimated median of **VMAXNISF_THY_I** calculated using the median, 97.5th, and 2.5th percentiles from Table A-5 ("VMAXTHYC_I") is 0.27, leading to minimal impact from uncertainty. However, using the (max-min)/(2*mean) of the percent iodine uptake from 14 pregnant subjects reported by Aboul-Khair et al. (1964) yields a variability estimate of 0.4, resulting in a moderate parameter variability impact on the model-predicted effect of perchlorate. However, it must also be noted that the correlation between **VMAXNISF_THY_I** and **CLFUI** obtained in the statistical analysis shows that the overall uncertainty in model predictions would be over-predicted if

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they were assumed to vary independently; a combination of high **CLFUI** and low **VMAXNISF_THY_I** (or vice-versa) is not consistent with the data. (In fact, estimates of these parameters tend to be highly correlated. See Section 4 of this Appendix.) Further, the calibration of the model to match TH levels in specific population percentiles corrects the model to some extent for uncertainty in these two iodide PK parameters. Therefore, their overall uncertainty is considered to be low.

Given the high sensitivity of model predictions to each of KMNIS_P, CLFUP, KMNIS_I, VMAXNISF_THY_I, and CLFUI (Table A-8), with **KMNIS_P** and **CLFUP** having absolute sensitivity coefficients of almost 1, the overall impact of their uncertainty is quite high. While (Greer, et al., 2002) provide extremely valuable data to inform these parameters, overall accuracy could be improved if a larger study were available.

Recently, Schlosser (2016) re-analyzed in vitro data for perchlorate's inhibition of iodide transport by the NIS and obtained a value of 5.9×10^4 ng/L for the Michaelis-Menten affinity constant (Km), quite similar to the 50th percentiles from the selected sampling strategy in Table A-6 (A2), 7.28×10^4 ng/L. Since the in vitro data are completely independent of Greer et al. (2002) and are from experiments where perchlorate concentration could be exactly controlled, they provide increased confidence that the statistically-derived range from this analysis includes the true median and that the rationale for selecting the reduced sample of individual subjects is justified. Use of the 2.5th percentile for **KMNIS_P** from Table A-6 (KM_TPNG, Method A2), should then provide reasonably health-protective model predictions.

Similarly, the choice of the 2.5th percentile of **CLFUP** from Table A-5 (CLUC_I), while not accounting for inter-individual variability, should provide health-protective predictions at a population level of analysis.

Uncertainty due to the parameter describing affinity of iodide for NIS, **KMNIS_I**, is not specifically addressed by the statistical analysis. However, because reasonable iodine ingestion rates result in iodide serum concentrations well below this Km, the rate of iodide uptake is effectively determined by the ratio **VMAXNISF_THY_I/KMNIS_I**, and from a mathematical standpoint the uncertainty (and variability) that are (can be) attributed to **VMAXNISF_THY_I** in fact apply to this ratio, since the Km was treated as fixed for the statistical analysis. Hence, uncertainty in **KMNIS_I** is not expected to contribute to overall model uncertainty beyond that already elucidated here.

4.2 FRT40 and CT4TAR

FRT40 defines the ratio of free/total T4 in the non-pregnant woman. It is expected to vary in the population. Since hormone levels also experience intra-individual variability, even if the measurement for a single sample is reasonably accurate, it would not necessarily represent that person's average. However, the population median and percentiles for fT4 and T4 obtained from the NHANES data should be reasonably accurate. Given the very high sensitivity coefficient, variability in the ratio is expected to be a significant component of inter-individual variability in sensitivity to perchlorate. Based on NHANES data for non-pregnant women, 2.5th, 50th and 97.5th percentile, the parameter variability is 0.34. While the range of fT4/T4 evaluated for pregnancy (~ ± 20%; see Figure A-36) can also be assumed to represent variability, there is no other convenient measure of uncertainty for this parameter, so its parameter uncertainty is set to 0.2 for this evaluation.

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CT4TAR is the "target" T4 concentration. When the script for model calibration is run, values of specific parameters are selected such that at the iodine intake level used for calibration (90 μg/d used for these analyses) the predicted T4 concentration matches the target with TSH signaling turned off. The TSH empirical curve is then normalized to its value at fT4 = CFT4TAR = CT4*FRT4 is equal to CT4TAR*FRT40, with the result that the signal is "neutral" (neither induces nor inhibits iodine uptake and TH production relative to the calibration point) when CT4 = CT4TAR (and FRT4 = FRT40, the value for the non-pregnant woman). Specifically, the model terms which are multiplied to the Vmax for iodide uptake and T4 and T3 production rates are set = 1, so these processes are neither induced nor inhibited when CT4 = CT4TAR and FRT4 = FRT40. In this way, the model continues to match CT4TAR prior to pregnancy when TSH signaling is turned on and iodine ingestion is at the level used for calibration, but responds with induction or inhibition when CT4 falls below or increases above CT4TAR. The functional result is that CT4TAR scales the TSH signaling strength, thereby giving it high influence on the predicted dose-response.

Since CT4TAR is set to fixed percentiles of the T4 distribution from NHANES, its value is known to a good level of precision. Model simulations for the non-pregnant woman would not match the target population percentile if CT4TAR was changed. Therefore, the parameter uncertainty is treated as ~ 0 for this analysis, although uncertainty in the overall TSH feedback strength may be high, and the parameter variability estimated from NHANES data for non-pregnant women is used: 0.26.

4.3 PTSHV and PTSHK

PTSHV is the coefficient which determines the strength of TSH signaling, hence the predicted dose-response is also highly sensitive to this parameter. In the model code there are in fact two such parameters, defining the separate effect of TSH on the Vmax for iodide uptake by the thyroid, PTSHV, and the effect of TSH on the production of T3 and T4, PTSHK. However, for this and most analyses presented here PTSHK = PTSHV, so PTSHV in fact reflects the effect on both iodide uptake and hormone production. The model was first evaluated assuming **PTSHV = 1**, which means that the strength of the TSH signal, or multiplicative change in the Vmax for iodide uptake and TH production constants, is directly proportional to the relative change in TSH from the value specified for calibration. For example, if TSH concentration doubles compared to the concentration used for calibration, then the Vmax and production rates are assumed to also double.

The 1T model effectively assumes that the relationship between TSH and fT4 is different for each individual or population percentile. Figure A-46 shows *median* TSH vs. fT4 levels from 14 different studies evaluating the changes in these parameters during pregnancy. There is a high level of variability within each study, as well as the inter-study differences shown in Figure A-46. These data are interpreted as implying that while there is a significant relationship between TSH and fT4 in any given individual (i.e., that person's TSH responds dynamically to variations in her fT4), the level of TSH at a given fT4 concentration, effectively the individual's calibration, varies widely between individuals. The fact that the NHANES data show little or no correlation between TSH and fT4, while clear trends due to pregnancy-related changes are observed, is considered evidence of this variability. (The relationship between TSH and fT4 is not assumed to be modulated by hCG during pregnancy, though the changes in fT4 induced by pregnancy affect TSH levels.) The lack of correlation in the NHANES data (non-pregnant women) is assumed to be due to the combination of inter-individual variability and the fact that each individual is only sampled once. To evaluate the validity of this assumption fully, serial observations would need to be made on individual subjects, so that the variation in her TSH in response to variation in her fT4 level is observed. However, the fact that the

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empirical curve from Hadlow et al. (2013), when scaled to individual data sets does an adequate job of matching the median TSH vs. fT4 data (Figure A-46) strongly suggests that it is valid.

The significant uncertainty with respect to TSH signaling in the model is with respect to the extent that a change in TSH levels impacts iodide uptake (Vmax) and T4 and T3 production; i.e., in the value of **PTSHV**. To evaluate this coefficient, matched measurements of TSH, iodide uptake, and T4 and T3 turnover would need to be made as these vary over time. Given the wide variability in observed TSH vs. fT4, serial samples in the same individual would likely be needed. A range of **PTSHV** was estimated from the NHANES data as being from (median TSH)/(97.5th percentile TSH) = 0.398 to (median TSH)/(2.5th percentile TSH) = 3.09. Using these values to estimate parameter uncertainty, (3.1-0.4)/(2*1) = 1.35. Given the approximate method in which the range of **PTSHV** was evaluated, and the possibility that there is a wide range of responsiveness to TSH feedback among individuals, this uncertainty is also assumed to represent potential variability. In combination with the high sensitivity to **PTSHV**, the resulting prediction variability and uncertainty is high.

It should be noted, however, that only ~ ¼ of the range is below the assumed median, **PTSHV = 1**. As shown in Table A-9, the further impact of reducing PTSHV from 0.4 to 0 on the perchlorate dose-response is a factor of 2 or less. **PTSHV** = 0 would imply an individual who's thyroid was completely non-responsive to TSH. One could assume that such an individual would already have thyroid disease, requiring medical intervention, whereas the purpose of this assessment is to evaluate the impact of perchlorate on otherwise healthy individuals. Given that model results used to derive the MCLG were generated using **PTSHV** = 0.398, the remaining uncertainty due to the fact that **PTSHV** might actually be lower still can be considered moderate.

4.4 CLUFT4 and KDEGT4F

The total rate of clearance of T4 is determined by the sum of **CLUFT4** and **KDEGT4F**, but the degradation path leads to T3 production with release of a single iodide ion (50% of degradation) or complete degradation with release of four iodide ions, which are then available for re-use by the thyroid. Urinary clearance completely removes the ions from the body while degradation releases some iodide, increasing serum iodide levels and so providing more iodide for the thyroid to use. This moderates the impact of increased degradation compared to the impact of increased clearance. Hence the sensitivity of the predicted perchlorate-fT4 dose-response to an increase in **KDEGT4F** is lower than an increase in **CLUFT4**. Data directly measuring T4 metabolism, or degradation, were not obtained.

Since Lumen et al. (2013) calibrated the value of both these parameters in development of the late-gestation model, they were likewise used for the current set of calibrations. However, the data on measured hormone levels are not sufficient to independently identify both parameters (and corresponding T3 parameters); either one has to be fixed or the relationship between them defined. When exploring an approach to rapidly calibrate the model for any given individual or data set, it was found that this could be more easily accomplished if **KDEGT4F** was assigned a fixed value and the inter-individual variation was achieved by varying **CLUFT4**. In particular, if **KDEGT4F** is set to 10% of the value obtained by Lumen et al. (2013), then the full range of observed T4 levels in NHANES could be described by varying CLUFT4, along with **KDEGT3F**, **KPRODT4F**, and **KPRODT3F**. Hence these parameters vary with the population percentile being described, but the uncertainty in their sum (**CLUFT4 + KDEGT4F**) reflects the uncertainty in the dose-response estimate for the specific population percentile described as occurring with iodine intake used for

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calibration (90 μg/d). Considering that data from 750 individuals were used to evaluate the percentiles, those thyroid hormone levels should be accurate representations of the population and the estimated total elimination rate is well supported by the data.

Nevertheless, a numerical estimate for the uncertainty and variability for **KDEGT4F** can be obtained from Kaptein, Moore, Ferguson, & Hoenig (1993), who reported a range for T4 degradation corresponding to a coefficient of variation (CV) of 0.26. The range of CLUFT4 between the 10th, median, and 90th percentile calibration sets is 41% of the median, so this value is used to quantify its variability, while assuming ~ 0 uncertainty since it is calibrated to each population percentile.

However, the variability in T4 (and T3) in the population is then a significant source of variability in the variability of sensitivity to perchlorate.

4.5 BW0 and VDFT40

Data for the volume of distribution for T4 in non-pregnant women, **VDFT40**, and its extrapolation into pregnancy were described in Section 1.4.7. While several data sets were identified, the resulting range in volumes was approximately ± 20% of the average. Fisher et al. (1971) reported a range for T4 volume of distribution corresponding to a CV of 0.14, hence the *variability* is characterized as 0.28. As shown in Figure A-31, a limited data set then indicates a decline in VDFT4 of 30-40% between GW 0 and GW 14, but given the small sample size and variation, the rate of decline with GW (slope of the regression) could easily be 50% greater or smaller than estimated. Since the average absolute SC for VDFT40 is 0.23, uncertainty in its value by 50% indicates a maximal impact of around 10%, which is modest. So the data supporting the volume of distribution appear to be adequate, though improved accuracy would reduce model uncertainty.

The changes in **BW** with pregnancy shown in Figure A-24 (lower panel) range from ~ 5 kg weight loss to over 5 kg weight gain, or 15% of a standard adult **BW** of 70 kg. Coupled with the variability in **BW** in the population and sensitivity ranging from 60-70%, the overall parameter variability is estimated to be 0.4 ((0.65+0.15)/2), it appears that the variation in BW before pregnancy and growth during pregnancy is a significant factor in population variability in perchlorate dose-response.

4.6 AOBT4

AOBT4 is an empirical regression parameter that defines the curvature in the gestation-dependent concentration of fT4 as described in Section 1.4.9. It is one component of the predicted variation in fT4/T4 (and fT3/T3), shown in Figure A-36. Since it is a direct factor in predicting fT4 levels during pregnancy, it has some sensitivity which increases with gestational age. A range of **AOBT4** was obtained by fitting a quadratic curve to several different data sets, after normalizing them to the study-specific fT4 concentration in non-pregnant controls. If one assumes that by normalizing fT4 to control levels, the between-study differences in analytic methods are minimized (i.e., that the relative change in fT4 is insensitive to analytic differences), then the inter-study differences in **AOBT4** might better represent population variability than uncertainty. However, we can't necessarily say which part of the range applies to a given individual or population percentile within the U.S., so in that regard it is still an uncertainty. Using the range of values obtained in Section 1.4.9, a parameter variability or uncertainty of 0.25 is obtained. For the purpose of this evaluation, it is assumed to apply to both variability and uncertainty.

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The range in predicted fT4 time-courses for pregnancy, shown in Figure A-57, only used the median value for this parameter. While the absolute upper and lower simulation sets do not match the upper/lower data sets shown, the trend with GW doesn't vary much between data sets, and use of the median value for **AOBT4** (and the corresponding linear term) appears adequate. However, model simulation results for use in the MCLG derivation assumed the median value of **AOBT4** for the population median prediction and the most negative value (leading to the lowest predicted fT4 later in the first trimester) to the population 10th percentile prediction, so some of the impact of this uncertainty is accounted for in comparing those sets of predictions.

4.7 QFC0 and QFTHY0

Cardiac output (QFC0) and tissue-specific blood flow (in this case, QFTHY for the thyroid) are generally assumed to be accurately known from physiological databases. However, as shown in Figure A-25, there is considerable variability between and within the various studies in which data were found for QFC0: (L-U)/(2*median) ~ 0.4. For the purpose of analysis, this value is assumed to represent parameter variability, with parameter uncertainty = 0.2. However, the sensitivity coefficients for these parameters were only marginally significant with pTSH = 1 and not significant with pTSH = 0.4. Therefore, reducing the uncertainty in these flows, including their trend in gestation, would not significantly improve overall dose-response uncertainty.

4.8 KHCG

KHCG is the proportionality constant between the hCG concentration during pregnancy and its stimulatory effect on the thyroid. The constant was estimated by using a linear regression against data on fT4 and hCG during pregnancy from Glinoer (1997), assuming that the variation in fT4 was due to the corresponding changes in hCG. An empirical relationship for changes in **VMAXNISF_THY_I** with gestational age based on variation in radio-iodide uptake was included separately in the model, based on the analysis of Clewell et al. (2007), although it might otherwise be presumed that hCG stimulates both NIS expression and TH production. Therefore, the direct functional application of hCG stimulation was only applied to T4 and T3 production: both were assumed to increase in proportion to the serum concentration of hCG, with **KHCG** being the proportionality constant. Considering that only 10 time-matched values of fT4 and hCG were used to estimate **KHCG** (Figure A-42) the uncertainty in its value might be considered high. However, comparison of 1T model predictions to TH changes during pregnancy show that the resulting model recapitulates the observed increases in total T4 and total T3 up to GW 16 fairly well (Figure A-57 and Figure A-58). Removing either the two highest hCG or 4 highest hCG points from Figure A-42 and revising the regression yields a range of slopes from 0.0038-0.0059 (ng/dL)/(kIU/L). Dividing this range by twice the slope obtained with all data included yields a parameter uncertainty of 0.26, which is used for this analysis.

Since **KHCG** multiplies the empirical curve fitted to the observed median hCG vs. GW from Korevaar et al. (2015), the variability and potential uncertainty in that curve and data should also be considered. Korevaar et al. (2015) is one component of the larger Generation R study conducted in the Netherlands Jaddoe et al. (2012), with samples taken from nearly 8200 pregnant women. It is judged to be a high quality study, and the sample size is sufficient to accurately identify the population median. The fact that the study did not consist of subjects from a U.S. population introduces some uncertainty, but considering that TH data from a number of countries are shown in Figure A-57 and Figure A-58 to be largely consistent, this additional uncertainty is also considered

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limited. Hence the uncertainty in the empirical curve for median hCG with gestation is considered low. However, using the data for 2.5th, median, and 97.5th percentiles of hCG in Figure A-41, an average parameter variability for hCG levels in the pregnant population is 0.85, and is used to represent variability for **KHCG.**

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Annex 1 – Regression Output Tables for Physiological Parameters

Table Annex-1: Nonlinear Regression Results for Changes in Cardiac Output with Gestation

Comparison of Fits	Can't calculate
Null hypothesis	Second order polynomial (quadratic)
Alternative hypothesis	One-phase association
P value	
Conclusion (alpha = 0.05)	Models have the same DF
Preferred model	One-phase association
F (DFn, DFd)	
Second order polynomial (quadratic)	
Best-fit values	
B0	302.4
B1	8.57
B2	-0.139
Std. Error	
B0	6.009
B1	0.6533
B2	0.01531
95% CI (profile likelihood)	
B0	290.6 to 314.2
B1	7.288 to 9.851
B2	-0.169 to -0.109
Goodness of Fit	
Degrees of Freedom	1724
R square (weighted)	0.1745
Weighted Sum of Squares ($1/Y^2$)	80.09
Sy.x	0.2155
One-phase association	
Best-fit values	
Y0	293.8
Plateau	434.5
K	0.1027
Tau	9.74
Half-time	6.751
Span	140.6
Std. Error	
Y0	6.537
Plateau	4.292
K	0.0135
Span	7.208
95% CI (profile likelihood)	
Y0	281 to 306.7
Plateau	426.8 to 444.2
K	0.07826 to 0.1328

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Tau	7.531 to 12.78
Half-time	5.22 to 8.857
Goodness of Fit	
Degrees of Freedom	1724
R square (weighted)	0.1832
Weighted Sum of Squares ($1/Y^2$)	79.87
Sy.x	0.2152
Constraints	
K	K > 0
Number of points	
# of X values	1727
# Y values analyzed	1727

Table Annex-2: Nonlinear Regression Results for Changes in Plasma Volume with Gestation

Comparison of Fits	
Null hypothesis	Second order polynomial (quadratic)
Alternative hypothesis	Third order polynomial (cubic)
P value	0.0012
Conclusion (alpha = 0.05)	Reject null hypothesis
Preferred model	Third order polynomial (cubic)
F (DFn, DFd)	10.56 (1, 3115)
Third order polynomial (cubic)	
Best-fit values	
B0	2.512
B1	0.004366
B2	0.001751
B3	-2.234e-005
Std. Error	
B0	0.02975
B1	0.006569
B2	0.000407
B3	6.874e-006
95% CI (profile likelihood)	
B0	2.454 to 2.571
B1	-0.008513 to 0.01725
B2	0.0009535 to 0.002549
B3	-3.582e-005 to -8.862e-006
Goodness of Fit	
Degrees of Freedom	3115
R square	0.4668
Absolute Sum of Squares	931.7
Sy.x	0.5469
Second order polynomial (quadratic)	
Best-fit values	
B0	2.473
B1	0.02338
B2	0.0004492
Std. Error	

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B0	0.02723
B1	0.002989
B2	7.135e-005
95% CI (profile likelihood)	
B0	2.42 to 2.527
B1	0.01752 to 0.02924
B2	0.0003093 to 0.0005891
Goodness of Fit	
Degrees of Freedom	3116
R square	0.465
Absolute Sum of Squares	934.9
Sy.x	0.5477
Number of points	
# of X values	3119
# Y values analyzed	3119

Table Annex-3: Nonlinear Regression Results for Changes in Percentage Hematocrit with Gestation

Comparison of Fits	
Null hypothesis	Second order polynomial (quadratic)
Alternative hypothesis	Third order polynomial (cubic)
P value	<0.0001
Conclusion (alpha = 0.05)	Reject null hypothesis
Preferred model	Third order polynomial (cubic)
F (DFn, DFd)	19.53 (1, 6766)
Third order polynomial (cubic)	
Best-fit values	
B0	39.4
B1	-0.04117
B2	-0.00898
B3	0.0001763
Std. Error	
B0	0.2675
B1	0.04675
B2	0.002506
B3	3.991e-005
95% CI (profile likelihood)	
B0	38.87 to 39.92
B1	-0.1328 to 0.05047
B2	-0.01389 to -0.004067
B3	9.811e-005 to 0.0002546
Goodness of Fit	
Degrees of Freedom	6766
R square	0.1169
Absolute Sum of Squares	103989
Sy.x	3.92
Second order polynomial (quadratic)	
Best-fit values	
B0	40.12

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B1	-0.2268
B2	0.001907
Std. Error	
B0	0.2127
B1	0.02051
B2	0.0004589
95% CI (profile likelihood)	
B0	39.7 to 40.53
B1	-0.2671 to -0.1866
B2	0.001007 to 0.002807
Goodness of Fit	
Degrees of Freedom	6767
R square	0.1143
Absolute Sum of Squares	104289
Sy.x	3.926
Number of points	
# of X values	6770
# Y values analyzed	6770

Table Annex-4: Linear Regression Comparison of Body Weight and Thyroid Volume

	Body Weight (kg)	Thy vol (ml)	Global (shared)
Comparison of Fits			
Null hypothesis			Slope same for all data sets
Alternative hypothesis			Slope different for each data set
P value			0.0517
Conclusion (alpha = 0.05)			Do not reject null hypothesis
Preferred model			Slope same for all data sets
F (DFn, DFd)			3.787 (1, 5935)
Slope different for each data set			
Best-fit values			
YIntercept	64.17	9.993	
Slope	0.05401	0.1102	
Std. Error			
YIntercept	0.09276	0.1445	
Slope	0.02233	0.01831	
95% CI (profile likelihood)			
YIntercept	63.99 to 64.36	9.71 to 10.28	
Slope	0.01024 to 0.09779	0.07433 to 0.1461	
Goodness of Fit			
Degrees of Freedom	3322	2613	
R square	0.001759	0.01368	
Absolute Sum of Squares	83052	54426	
Sy.x	5	4.564	
Slope same for all data sets			
Best-fit values			
YIntercept	64.13	10.15	
Slope	0.08512	0.08512	0.08512
Std. Error			
YIntercept	0.08614	0.1296	

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Slope	0.01437	0.01437	0.01437
95% CI (profile likelihood)			
YIntercept	63.96 to 64.3	9.895 to 10.4	
Slope	0.05695 to 0.1133	0.05695 to 0.1133	0.05695 to 0.1133
Goodness of Fit			
Degrees of Freedom			5936
R square	0.001175	0.01297	0.9683
Absolute Sum of Squares	83100	54466	137566
Sy.x			4.814
Constraints			
Slope	Slope is shared	Slope is shared	
Number of points			
# of X values	3366	2642	
# Y values analyzed	3324	2615	

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1.1 Approximate Uncertainty and Variability Analysis of Key Parameters

A semi-quantitative analysis of the uncertainty and variability of the parameters identified in the Local Sensitivity Analysis (LSA) follows. The local sensitivity of *all* model parameters was evaluated for the LSA, but only parameters with a sensitivity coefficient (SC) whose absolute value is greater than 0.1 for at least one time-point/population percentile were listed in Table A-8 (i.e., the SCs for other parameters were evaluated but not shown since |SC| < 0.1). This uncertainty/variability (U/V) analysis addresses that subset of model parameters.

The objective of the U/V analysis is to estimate the degree of variability and uncertainty in key parameters and the potential magnitude of their impact on model predictions. However, except for the parameters addressed by the Bayesian analysis of [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Greer</Author><Year>2002</Year><RecNum>2835</RecNum><IDText>51202</IDText><DisplayText>Greer et al. (2002)</DisplayText><record><rec-number>2835</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2835</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M. A.</author><author>Goodman, G.</author><author>Pleus, R. C.</author><author>Greer, S. E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>927-937</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><label>51202</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.02110927</url></related-urls></urls><electronic-resource-num>10.1289/ehp.02110927</electronic-resource-num><language>English</language></record></Cite></EndNote>] data, statistically rigorous uncertainty ranges have not been defined for the parameters. In several cases, representative upper and lower values were obtained during parameter estimation; e.g., by fitting an empirical curve for pregnancy-related changes to the highest or lowest data set. These ranges were not defined in a statistically rigorous manner. For other parameters or curves, such as BW increase with pregnancy, a precise range was not obtained. Nevertheless, it is possible to obtain a rough estimate of the range compared to the central estimate by considering the range of the data, and the number of data sets supporting a specific parameters or empirical curves. This approach seeks to identify the maximal impact of uncertainty or variability in any given parameter on model predictions, when varied one at a time.

By multiplying the estimated variability or uncertainty by the average or maximum absolute sensitivity coefficient (SC) obtained in the LSA, a semi-quantitative measure of the overall impact of the variability or uncertainty can be estimated. For example, a parameter whose SC is

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0.2 has the potential to impact model predictions. But if the data indicate that the uncertainty is ± 50% of the mean value, which may seem large, the impact of that uncertainty is only expected to be ± 10% of the mean model output (50% x 0.2).

For some parameters such as maternal BW, the uncertainty for any given individual is quite small. BW can be easily measured with good accuracy. But there is inherent population variability that cannot be reduced by collection of additional data. For those parameters that significantly impact the perchlorate dose-response which are inherently variable, one must then conclude that there is resulting variability in the sensitivity of individuals in the population to perchlorate.

[REF _Ref488307099 \h]0 summarizes the findings of this uncertainty and variability evaluation. The sensitivity column provides the range (and an average) of absolute SCs from the preceding LSA. The parameter variability column provides a relative range, (max – min)/(2*median) or 2 times the coefficient of variation (2*CV), for the *variability* in parameters for which such estimates are possible and where the parameter range or variance is reasonably attributed to inter-individual variability. The impact of variability is estimated by multiplying the variability factor by the *maximum* absolute sensitivity, since this incorporates variability in iodine intake and gestation week evaluated. Parameter *uncertainty* is similarly calculated, where possible, and the resulting relative range can be reasonably attributed to uncertainty (lack of information or imprecision) that might be reduced through further collection of data. The impact of uncertainty was calculated using the average absolute sensitivity (times the uncertainty factor), as a measure of average impact. A parameter may have wide variability in the population, and this is not a matter of imperfect knowledge, and that variability may result in inter-individual variability in sensitivity to perchlorate.

Table A-[SEQ Table * ARABIC]0. Uncertainty and Variability Summary with Potential Impact on Dose-Response

Parameters with maximum |SC| > 0.1 (Table A-8)	Absolute SC (Table A-8) *	Variability		Uncertainty	
		Parameter variability	Potential impact	Parameter uncertainty	Potential impact
KMNIS_P‡	0.96-0.98 (0.97)	~ 0	~ 0	0.86	**0.8**
CLFUP‡	0.95-0.98 (0.97)	0.82	**0.8**	0.16	0.2
FRT40	1.14-1.94 (1.45)	0.34	**0.7**	0.2	0.3
CT4TAR	0.6-0.93 (0.76)	0.26	0.2	~ 0	< 0.1
PTSHV, PTSHK‡†	0.38-0.72 (0.54)	1.35	**1**	1.35	**0.7**
CLFUI	0.36-0.82 (0.55)	0.82	**0.7**	0.2	0.1
VMAXNISF_THY_I (-KMNIS_I)	0.37-0.65 (0.48)	0.4 (~ 0)	0.3 (~ 0)	0.27 (~ 0)	0.1 (~ 0)
CLUFT4	0.2-0.91 (0.46)	0.41	0.4	~ 0	~ 0

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KDEGT4F†	0.09-0.28 (0.18)	0.52	0.1	0.52	< 0.1
BW0	0.57-0.9 (0.7)	0.4	0.4	~ 0	~ 0
VDFT40	0.09-0.36 (0.23)	0.28	0.1	0.5	0.1
AOBT4	0-0.24 (0.1)	0.25	< 0.1	0.25	< 0.1
QFC0, QFTHY0	0-0.16 (0.07)	0.4	< 0.1	0.2	< 0.1
KHCG	0-0.13 (0.06)	0.85	0.1	0.26	< 0.1

* Values are range of absolute sensitivity coefficients (SCs) across iodine intake and gestation times evaluated (numerical average of absolute sensitivities)

‡ Lower bound estimates of KMNIS_P and CLFUP (5th percentile of the estimated distribution for the median) and of PTSHV and PTSHK (approximate lower bound = 0.4), which result in higher sensitivity to perchlorate than median estimates, were evaluated and used to derive the MCLG. The likelihood that KMNIS_P or CLFUP are significantly less than the 5th percentiles used is considered low. Likewise, the likelihood that PTSHV and PTSHK are less than 0.4 is considered low. Hence the remaining uncertainty is qualified as low.

†For PTSHV, PTSHK, and KDEGT4F one cannot distinguish variability and uncertainty due to lack of data. The potential impact is calculated for both, but the combined uncertainty and variability would likely be less than obtained by adding these estimates.

The discussion below generally addresses the parameters in order of sensitivity from highest (average) to lowest, but parameters are also grouped according to the model component that they impact.

1.1.1 KMNIS_P, CLFUP, KMNIS_I, VMAXNISF_THY_I, and CLFUI

With the exception of the Vmax, this set of pharmacokinetic parameters are those analyzed in Section 1 of the appendix. This was a rigorous statistical analysis making use of the data from the well-defined, clinical [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Greer</Author><Year>2002</Year><RecNum>2835</RecNum><IDText>51202</IDText><DisplayText>Greer et al. (2002)</DisplayText><record><rec-number>2835</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2835</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M. A.</author><author>Goodman, G.</author><author>Pleus, R. C.</author><author>Greer, S. E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-

1>Environ Health Perspect</abbr-1></alt-periodical><pages>927-937</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><label>51202</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.02110927</url></related-urls></urls><electronic-resource-num>10.1289/ehp.02110927</electronic-resource-num><language>English</language></record></Cite></EndNote>] study. While [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Greer</Author><Year>2002</Year><RecNum>2835</RecNum><IDText>51202</IDText><DisplayText>Greer et al. (2002)</DisplayText><record><rec-number>2835</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2835</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M. A.</author><author>Goodman, G.</author><author>Pleus, R. C.</author><author>Greer, S. E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>927-937</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><label>51202</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.02110927</url></related-urls></urls><electronic-resource-num>10.1289/ehp.02110927</electronic-resource-num><language>English</language></record></Cite></EndNote>] provides data of a quality and value not often available for toxic chemicals and measures the effect of perchlorate on the key precursor effect, iodide uptake inhibition, the number of female subjects is limited: only 4 per dose group. Even if data from both male and female subjects were used, the total number (8 per dose group) would be inadequate to characterize *variability* in the U.S. population. But other data sources can be used to evaluate variability in urinary clearance (**CLFUP** and **CLFUI**) and iodine uptake (**VMAXNISF_THY_I**).

The enzyme affinity parameters, **KMNIS_P** and **KMNIS_I**, are intrinsic properties of the NIS, for which there is no known polymorphism (the molecular structure does not vary in the population) and the iodide and perchlorate anions. Therefore, no inter-individual variability is expected for these parameters in the general population, and the estimated *uncertainty* in the value from the [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Greer</Author><Year>2002</Year><RecNum>2835</RecNum><IDText>51202</IDText><DisplayText>Greer et al. (2002)</DisplayText><record><rec-number>2835</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2835</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer,

M. A.</author><author>Goodman, G.</author><author>Pleus, R. C.</author><author>Greer, S. E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>927-937</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><label>51202</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.02110927</url></related-urls></urls><electronic-resource-num>10.1289/ehp.02110927</electronic-resource-num><language>English</language></record></Cite></EndNote>] data should adequately represent the overall uncertainty in the parameter. Only the top 3 dose groups showed a significant effect on iodide uptake, hence informing **KMNIS_P**, and because of the presumed induction of NIS in the top group, data from only the middle two groups, were combined to estimate that parameter and the range of estimated population median values (Table A-3 and Table A-4). In particular, the 2.5th sampling percentile for the median from the six subjects with reasonably consistent values (set A2, "KM_TPNG" in Table A-4) was selected for use. Therefore, the uncertainty is characterized as (97.5th – 2.5th)/(2*50th) percentiles from that sample: 0.86.

The uncertainty factors for **CLFUP** and **CLFUI** based on results in Table A-3 ("CLUC_P" and "CLUC_I") are only 0.16 and 0.2, respectively. But the range iodide clearance reported by [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Aboul-Khair</Author><Year>1964</Year><RecNum>2426</RecNum><IDText>2140787</IDText><DisplayText>Aboul-Khair et al. (1964)</DisplayText><record><rec-number>2426</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2426</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Aboul-Khair, S. A.</author><author>Crooks, J.</author><author>Turnbull, A. C.</author><author>Hytten, F. E.</author></authors></contributors><titles><title>The physiological changes in thyroid function during pregnancy</title><secondary-title>Clinical Science</secondary-title><alt-title>Clin Sci (Lond)</alt-title><short-title>Clinical Science</short-title></titles><periodical><full-title>Clinical Science</full-title><abbr-1>Clin Sci (Lond)</abbr-1></periodical><alt-periodical><full-title>Clinical Science</full-title><abbr-1>Clin Sci (Lond)</abbr-1></alt-periodical><pages>195-207</pages><volume>27</volume><dates><year>1964</year></dates><isbn>ISSN 0143-5221
EISSN 1470-8736</isbn><label>2140787</label><urls></urls><language>English</language></record></Cite></EndNote>] indicating inter-individual variation, which is presumed to also apply to

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perchlorate, is a coefficient of variation (CV) of 41% among 13 non-pregnant control subjects, leading to a variability factor of 0.82.

The uncertainty for the estimated median of **VMAXNISF_THY_I** from Table A-3 ("VMAXTHYC_I") is 0.27, leading to minimal impact from uncertainty. However, using the (max-min)/(2*mean) of the percent iodine uptake from 14 pregnant subjects reported by [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Aboul-Khair</Author><Year>1964</Year><RecNum>2426</RecNum><IDText>2140787</IDText><DisplayText>Aboul-Khair et al. (1964)</DisplayText><record><rec-number>2426</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2426</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Aboul-Khair, S. A.</author><author>Crooks, J.</author><author>Turnbull, A. C.</author><author>Hytten, F. E.</author></authors></contributors><titles><title>The physiological changes in thyroid function during pregnancy</title><secondary-title>Clinical Science</secondary-title><alt-title>Clin Sci (Lond)</alt-title><short-title>Clinical Science</short-title></titles><periodical><full-title>Clinical Science</full-title><abbr-1>Clin Sci (Lond)</abbr-1></periodical><alt-periodical><full-title>Clinical Science</full-title><abbr-1>Clin Sci (Lond)</abbr-1></alt-periodical><pages>195-207</pages><volume>27</volume><dates><year>1964</year></dates><isbn>ISSN 0143-5221
EISSN 1470-8736</isbn><label>2140787</label><urls></urls><language>English</language></record></Cite></EndNote>] yields a variability estimate of 0.4, resulting in a moderate impact on variability in perchlorate impact. However, it must also be noted that the correlation between **VMAXNISF_THY_I** and **CLFUI** obtained in the statistical analysis shows that the overall uncertainty in model predictions would be over-predicted if they were assumed to vary independently; a combination of high **CLFUI** and low **VMAXNISF_THY_I** is not consistent with the data. Further, the calibration of the model to match TH levels in specific population percentiles corrects the model to some extent for uncertainty in these two iodide PK parameters. Therefore, their overall uncertainty is considered to be low.

Given the high sensitivity of model predictions to each of these parameters (Table A-9), with **KMNIS_P** and **CLFUP** having absolute sensitivity coefficients of almost 1, the overall impact of their uncertainty is quite high. While [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Greer</Author><Year>2002</Year><RecNum>2835</RecNum><IDText>51202</IDText><DisplayText>Greer et al. (2002)</DisplayText><record><rec-number>2835</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2835</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M. A.</author><author>Goodman, G.</author><author>Pleus, R. C.</author><author>Greer, S. E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health

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Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>927-937</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><label>51202</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.02110927</url></related-urls></urls><electronic-resource-num>10.1289/ehp.02110927</electronic-resource-num><language>English</language></record></Cite></EndNote>] provide extremely valuable data to inform these parameters, overall accuracy could be improved if a larger study were available.

Recently, [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Schlosser</Author><Year>2016</Year><RecNum>2378</RecNum><IDText>3222140</IDText><DisplayText>Schlosser (2016)</DisplayText><record><rec-number>2378</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2378</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schlosser, P. M.</author></authors></contributors><titles><title>Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter based on in vitro and human in vivo data</title><secondary-title>Journal of Applied Toxicology</secondary-title><alt-title>J Appl Toxicol</alt-title><short-title>Journal of Applied Toxicology</short-title></titles><periodical><full-title>Journal of Applied Toxicology</full-title><abbr-1>J Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Journal of Applied Toxicology</full-title><abbr-1>J Appl Toxicol</abbr-1></alt-periodical><pages>1531-1535</pages><volume>36</volume><number>12</number><dates><year>2016</year></dates><isbn>ISSN 0260-437X
EISSN 1099-1263</isbn><label>3222140</label><work-type>Review</work-type><urls><related-urls><url>http://dx.doi.org/10.1002/jat.3337</url></related-urls></urls><electronic-resource-num>10.1002/jat.3337</electronic-resource-num><language>English</language></record></Cite></EndNote>] re-analyzed in vitro data for perchlorate's inhibition of NIS and obtained a value of 5.9×10^4 ng/L, quite similar to the 50th percentiles from the selected sampling strategy in [REF _Ref485210738 \h] (A2), 7.3×10^4 ng/L. Since the in vitro data are completely independent of [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Greer</Author><Year>2002</Year><RecNum>2835</RecNum><IDText>51202</IDText><DisplayText>Greer et al. (2002)</DisplayText><record><rec-number>2835</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2835</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M. A.</author><author>Goodman, G.</author><author>Pleus, R. C.</author><author>Greer, S. E.</author></authors></contributors><titles><title>Health effects assessment for

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environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title><alt-title>Environ Health Perspect</alt-title><short-title>Environmental Health Perspectives</short-title></titles><periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></periodical><alt-periodical><full-title>Environmental Health Perspectives</full-title><abbr-1>Environ Health Perspect</abbr-1></alt-periodical><pages>927-937</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><isbn>ISSN 0091-6765
EISSN 1552-9924</isbn><label>51202</label><urls><related-urls><url>http://dx.doi.org/10.1289/ehp.02110927</url></related-urls></urls><electronic-resource-num>10.1289/ehp.02110927</electronic-resource-num><language>English</language></record></Cite></EndNote>] and are from experiments where perchlorate concentration could be exactly controlled, they provide increased confidence that statistical range from this analysis includes the true median and that the rationale for selecting the reduced sample of individual subjects is justified. Use of the 2.5th percentile for **KMNIS_P** from Table A-4 (KM_TPNG, Method A2), should then provide reasonably health-protective model predictions.

Similarly, the choice of the 2.5th percentile of **CLFUP** from Table A-3 (CLUC_I), while not accounting for inter-individual variability, should provide health-protective predictions at a population level of analysis.

Uncertainty due to the affinity of iodide for NIS, **KMNIS_I**, is not specifically addressed by the statistical analysis. However, because iodide serum concentrations remain well below this Km, the rate of iodide uptake is effectively determined by the ratio **VMAXNISF_THY_I/KMNIS_I**, and from a mathematical standpoint the uncertainty (and variability) that are (can be) attributed to **VMAXNISF_THY_I** in fact apply to this ratio, since the Km was treated as fixed for the statistical analysis. Hence, uncertainty in **KMNIS_I** is not expected to contribute to overall model uncertainty beyond that already elucidated here.

1.1.2 FRT40 and CT4TAR

FRT40 defines the ratio of free/total T4 in the non-pregnant woman. It is expected to vary in the population, hence is a source of variability. Since hormone levels also experience intra-individual variability, even if the measurement for a single sample is reasonably accurate, it would not necessarily represent that person's average. However, the population median and percentiles for fT4 and T4 obtained from the NHANES data should be reasonably accurate. Given the very high sensitivity coefficient, variability in the ratio is expected to be a significant component of inter-individual variability in sensitivity to perchlorate. Based on NHANES data for non-pregnant women, 2.5th, 50th and 97.5th percentile, the variability factor is 0.34. While the range of fT4/T4 evaluated for pregnancy (~ ± 20%; see Figure A-36) can also be assumed to represent variability, parameter uncertainty will be set to 0.2 for this evaluation.

CT4TAR is the "target" T4 concentration. When the script for model calibration is run, values of specific parameters are selected such that at the iodine intake level used for calibration (90

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μg/d used for these analyses) the predicted T4 concentration matches the target with TSH signaling turned off. The TSH empirical curve is then normalized to its value at fT4 = CFT4TAR = CT4*FRT4 is equal to CT4TAR*FRT40, with the result that the signal is "neutral" (neither induces nor inhibits iodine uptake and TH production relative to the calibration point) when CT4 = CT4TAR (and FRT4 = FRT40, the value for the non-pregnant woman). Specifically, the model terms which multiplies the Vmax for iodide uptake and T4 and T3 production rates are set = 1, so these processes are neither induced nor inhibited when CT4 = CT4TAR and FRT4 = FRT40. In this way the model will continue to match CT4TAR prior to pregnancy when TSH signaling is turned on and iodine ingestion is at the level used for calibration, but will respond with induction or inhibition when CT4 falls below or increases above CT4TAR. The functional result is that CT4TAR scales the TSH signaling strength, thereby giving it high influence on the predicted dose-response.

Since CT4TAR is set to fixed percentiles of the T4 distribution from NHANES, its value is known to a good level of precision. Model simulations for the non-pregnant woman would not match the target population percentile if CT4TAR was changed. Therefore, the uncertainty factor is treated as ~ 0 for this analysis, although uncertainty in the overall TSH feedback strength may be high, and the variability factor estimated from NHANES data for non-pregnant women will be used: 0.26.

1.1.3 PTSHV and PTSHK

PTSHV is the coefficient which determines the strength of TSH signaling, hence the predicted dose-response is also highly sensitive to this parameter. In the model code there are in fact two such parameters, defining the separate effect of TSH on the Vmax for iodide uptake by the thyroid, PTSHV, and the effect of TSH on the production of T3 and T4, PTSHK. However, for this and most analyses presented here PTSHK = PTSHV, so PTSHV in fact reflects the effect on both iodide uptake and hormone production. The model was first evaluated assuming **PTSHV = 1**, which means that the strength of the TSH signal, or multiplicative change in the Vmax for iodide uptake and TH production constants, is directly proportional to the relative change in TSH from the value specified for calibration. For example, if TSH concentration doubles compared to the concentration used for calibration, then the Vmax and production rates are assumed to also double.

The 1T model effectively assumes that the relationship between TSH and fT4 is different for each individual or population percentile. Figure A-46 shows *median* TSH vs. fT4 levels from 14 different studies evaluating the changes in these parameters during pregnancy. There is a high level of variability within each study, as well as the inter-study differences shown in Figure A-46. These data are interpreted as implying that while there is a significant relationship between TSH and fT4 in any given individual (i.e., that person's TSH responds dynamically to variations in her fT4), the level of TSH at a given fT4 concentration, effectively the individual's calibration, varies widely between individuals. The fact that the NHANES data show little or no correlation between TSH and fT4, while clear trends due to pregnancy-related changes are observed, is considered evidence of this variability. (The relationship between TSH and fT4 is

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not assumed to be modulated by hCG during pregnancy, though the changes in fT4 induced by pregnancy affect TSH levels.) The lack of correlation in the NHANES data (non-pregnant women) is assumed to be due to the combination of inter-individual variability and the fact that each individual is only sampled once. To evaluate the validity of this assumption fully, serial observations would need to be made on individual subjects, so that the variation in her TSH in response to variation in her fT4 level is observed. However, the fact that the empirical curve from [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Hadlow</Author><Year>2013</Year><RecNum>3207</RecNum><IDText>3645386</IDText><DisplayText>Hadlow et al. (2013)</DisplayText><record><rec-number>3207</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">3207</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hadlow, N. C.</author><author>Rothacker, K. M.</author><author>Wardrop, R.</author><author>Brown, S. J.</author><author>Lim, E. M.</author><author>Walsh, J. P.</author></authors></contributors><titles><title>The relationship between TSH and free T in a large population is complex and nonlinear and differs by age and sex</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>2936-2943</pages><volume>98</volume><number>7</number><dates><year>2013</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><label>3645386</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2012-4223</url></related-urls></urls><electronic-resource-num>10.1210/jc.2012-4223</electronic-resource-num><language>English</language></record></Cite></EndNote>], when scaled to individual data sets does an adequate job of matching the median TSH vs. fT4 data (Figure A-46) strongly suggests that it is valid.

The significant uncertainty with respect to TSH signaling in the model is with respect to the extent that a change in TSH levels impacts iodide uptake (Vmax) and T4 and T3 production; i.e., in the value of **PTSHV**. To evaluate this coefficient, matched measurements of TSH, iodide uptake, and T4 and T3 turnover would need to be made as these vary over time. Given the wide variability in observed TSH vs. fT4, serial samples in the same individual would likely be needed. A range of **PTSHV** was estimated from the NHANES data as being from (median TSH)/(97.5th percentile TSH) = 0.398 to (median TSH)/(2.5th percentile TSH) = 3.09. Using these values to estimate an uncertainty factor, (3.1-0.4)/(2*1) = 1.35. Given the approximate method in which the range of **PTSHV** was evaluated, and the possibility that there is a wide range of responsiveness to TSH feedback among individuals, this factor is also assumed to

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represent potential variability. In combination with the high sensitivity to **PTSHV**, the resulting prediction variability and uncertainty is high.

It should be noted, however, that only ~ ¼ of the range is below the assumed median, **PTSHV = 1**. As shown in Table A-9, the further impact of reducing PTSHV from 0.4 to 0 on the perchlorate dose-response is a factor of 2 or less. **PTSHV** = 0 would imply an individual who's thyroid was completely non-responsive to TSH. One could assume that such an individual would already have thyroid disease, requiring medical intervention, whereas the purpose of this assessment is to evaluate the impact of perchlorate on otherwise healthy individuals. Given that model results used to derive the MCLG were generated using **PTSHV** = 0.398, the remaining uncertainty due to the fact that **PTSHV** might actually be lower still can be considered moderate.

1.1.4 CLUFT4 and KDEGT4F

The total rate of clearance of T4 is determined by the sum of **CLUFT4** and **KDEGT4F**, but the degradation path leads to T3 production with release of a single iodide ion (50% of degradation) or complete degradation with release of four iodide ions, which are then available for re-use by the thyroid. Urinary clearance completely removes the ions from the body while degradation releases some iodide, increasing serum iodide levels and so providing more iodide for the thyroid to use. This moderates the impact of increased degradation compared to the impact of increased clearance. Hence the sensitivity of the predicted perchlorate-fT4 dose-response to an increase in **KDEGT4F** is lower than an increase in **CLUFT4**. Data directly measuring T4 metabolism, or degradation, were not obtained.

Since [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Lumen</Author><Year>2013</Year><RecNum>1837</RecNum><IDText>1578562</IDText><DisplayText>Lumen et al. (2013)</DisplayText><record><rec-number>1837</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">1837</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>Mattie, D. R.</author><author>Fisher, J. W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>320-341</pages><volume>133</volume><number>2</number><dates><year>2013</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><label>1578562</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kft078</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num><language>English</language></record></Cite></EndNote>] calibrated the value of both these parameters in development of the late-gestation model, they were likewise used for the

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current set of calibrations. However, the data on measured hormone levels are not sufficient to independently identify both parameters (and corresponding T3 parameters); either one has to be fixed or the relationship between them defined. When exploring an approach to rapidly calibrate the model for any given individual or data set, it was found that this could be more easily accomplished if **KDEGT4F** was assigned a fixed value and the inter-individual variation was achieved by varying **CLUFT4**. In particular, if **KDEGT4F** is set to 10% of the value obtained by [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Lumen</Author><Year>2013</Year><RecNum>1837</RecNum><IDText>1578562</IDText><DisplayText>Lumen et al. (2013)</DisplayText><record><rec-number>1837</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">1837</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>Mattie, D. R.</author><author>Fisher, J. W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title><alt-title>Toxicol Sci</alt-title><short-title>Toxicological Sciences</short-title></titles><periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></periodical><alt-periodical><full-title>Toxicological Sciences</full-title><abbr-1>Toxicol Sci</abbr-1></alt-periodical><pages>320-341</pages><volume>133</volume><number>2</number><dates><year>2013</year></dates><isbn>ISSN 1096-6080
EISSN 1096-0929</isbn><label>1578562</label><urls><related-urls><url>http://dx.doi.org/10.1093/toxsci/kft078</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num><language>English</language></record></Cite></EndNote>], then the full range of observed T4 levels in NHANES could be described by varying CLUFT4, along with **KDEGT3F**, **KPRODT4F**, and **KPRODT3F**. Hence these parameters vary with the population percentile being described, but the uncertainty in their sum (**CLUFT4 + KDEGT4F**) reflects the uncertainty in the estimate of the specific population percentile described as occurring with iodine intake used for calibration (90 μg/d). Considering that data from 750 individuals were used to evaluate the percentiles, those thyroid hormone levels should be accurate representations of the population and the estimated total elimination rate is well supported by the data.

Nevertheless, a numerical estimate for the uncertainty and variability for **KDEGT4F** can be obtained from [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Kaptein</Author><Year>1993</Year><RecNum>2652</RecNum><IDText>2140845</IDText><DisplayText>Kaptein et al. (1993)</DisplayText><record><rec-number>2652</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2652</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kaptein, E. M.</author><author>Moore, G. E.</author><author>Ferguson, D. C.</author><author>Hoenig, M.</author></authors></contributors><titles><title>Thyroxine and triiodothyronine distribution

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and metabolism in thyroxine-replaced athyreotic dogs and normal humans</title><secondary-title>American Journal of Physiology</secondary-title><alt-title>Am J Physiol</alt-title><short-title>American Journal of Physiology</short-title></titles><periodical><full-title>American Journal of Physiology</full-title><abbr-1>Am J Physiol</abbr-1></periodical><alt-periodical><full-title>American Journal of Physiology</full-title><abbr-1>Am J Physiol</abbr-1></alt-periodical><pages>E90-100</pages><volume>264</volume><number>1</number><dates><year>1993</year></dates><isbn>ISSN 0002-9513
EISSN 2163-5773</isbn><label>2140845</label><urls></urls><language>English</language></record></Cite></EndNote>], who reported a range for T4 degradation corresponding to a coefficient of variation (CV) of 0.26. The range of CLUFT4 between the 10th, median, and 90th percentile calibration sets is 41% of the median, so this value will be used to quantify its variability, while assuming ~ 0 uncertainty since it is calibrated to each population percentile.

However, the variability in T4 (and T3) in the population will then be a significant source of variability in the variability of sensitivity to perchlorate.

1.1.5 BW0 and VDFT40

Data for the volume of distribution for T4 in non-pregnant women, **VDFT40**, and its extrapolation into pregnancy were described in Section [REF _Ref483909962 \r \h * MERGEFORMAT]. While several data sets were identified, the resulting volumes range in values was approximately ± 20%. [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Fisher</Author><Year>1971</Year><RecNum>2434</RecNum><IDText>2140816</IDText><DisplayText>Fisher et al. (1971)</DisplayText><record><rec-number>2434</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2434</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fisher, D. A.</author><author>Oddie, T. H.</author><author>Thompson, C. S.</author></authors></contributors><titles><title>Thyroidal thyronine and non-thyronine iodine secretion in euthyroid subjects</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title><short-title>Journal of Clinical Endocrinology and Metabolism</short-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></periodical><alt-periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title><abbr-1>J Clin Endocrinol Metab</abbr-1></alt-periodical><pages>647-652</pages><volume>33</volume><number>4</number><dates><year>1971</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><label>2140816</label><urls></urls><language>English</language></record></Cite></EndNote>] reported a range for T4 volume of distribution corresponding to a CV of 0.14, hence the *variability* is characterized as 0.28. As shown in Figure A-31, a limited data set then indicates a decline in VDFT4 of 30-40% between GW 0 and GW 14, but given the small sample size and variation, the rate of decline with GW (slope of the regression) could easily be 50%

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greater or smaller than estimated. Since the average absolute SC for VDFT40 is 0.23, uncertainty in its value by 50% indicates a maximal impact of around 10%, which is modest. So the data supporting the volume of distribution appear to be adequate, though improved accuracy would reduce model uncertainty.

The changes in **BW** with pregnancy shown in Figure A-24 (lower panel) range from ~ 5 kg weight loss to over 5 kg weight gain, or 15% of a standard adult **BW** of 70 kg. Coupled with the variability in **BW** in the population and sensitivity ranging from 60-70%, the overall factor for variability is estimated to be 0.4 ((0.65+0.15)/2), it appears that the variation in BW before pregnancy and growth during pregnancy will be a significant factor in population variability in responsiveness to perchlorate.

1.1.6 AOBT4

AOBT4 is an empirical regression parameter that defines the curvature in the gestation-dependent concentration of fT4 as described in Section 2.3.9. It is one component of the predicted variation in fT4/T4 (and fT3/T3), shown in Figure A-36. Since it is a direct factor in predicting fT4 levels during pregnancy, it has some sensitivity which increases with gestational age. A range of **AOBT4** was obtained by fitting a quadratic curve to several different data sets, after normalizing them to the study-specific fT4 concentration in non-pregnant controls. If one assumes that by normalizing fT4 to control levels, the between-study differences in analytic methods are minimized (i.e., that the relative change in fT4 is insensitive to analytic differences), then the inter-study differences in **AOBT4** might better represent population variability than uncertainty. However, we can't necessarily say which part of the range applies to a given individual or population percentile within the U.S., so in that regard it is still an uncertainty. Using the range of values obtained in Section 2.3.9, a variability or uncertainty factor of 0.25 is obtained. For the purpose of this evaluation, it will be assumed to apply to both factors.

The range in predicted fT4 time-courses for pregnancy, shown in Figure A-57, only used the median value for this parameter. While the absolute upper and lower simulation sets do not match the upper/lower data sets shown, the trend with GW doesn't vary much between data sets, and use of the median value for **AOBT4** (and the corresponding linear term) appears adequate. However, model simulation results for use in the MCLG derivation assumed the median value of **AOBT4** for the population median prediction and the most negative value (leading to the lowest predicted fT4 later in the first trimester) to the population 10th percentile prediction, so some of the impact of this uncertainty is accounted for in comparing those sets of predictions.

1.1.7 QFC0 and QFTHY0

Cardiac output (QFC0) and tissue-specific blood flow (in this case, QFTHY for the thyroid) are generally assumed to be accurately known from physiological databases. However, as shown in Figure A-25, there is considerable variability between and within the various studies in which data were found for QFC0: (max-min)/(2*median) ~ 0.4. For the purpose of analysis, this factor is assumed to represent variability, with an uncertainty factor of 0.2. However, the sensitivity coefficients for these parameters were only marginally significant with pTSH = 1 and not

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significant with pTSH = 0.4. Therefore, reducing the uncertainty in these flows, including their trend in gestation, would not significantly improve overall model uncertainty.

1.1.8 KHCG

KHCG is the proportionality constant between the hCG concentration during pregnancy and its stimulatory effect on the thyroid. The constant was estimated by using a linear regression against data on fT4 and hCG during pregnancy from [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Glinoer</Author><Year>1997</Year><RecNum>1984</RecNum><IDText>16513</IDText><DisplayText>Glinoer (1997)</DisplayText><record><rec-number>1984</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">1984</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Glinoer, D.</author></authors></contributors><titles><title>The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology</title><secondary-title>Endocrine Reviews</secondary-title><alt-title>Endocr Rev</alt-title><short-title>Endocrine Reviews</short-title></titles><periodical><full-title>Endocrine Reviews</full-title><abbr-1>Endocr Rev</abbr-1></periodical><alt-periodical><full-title>Endocrine Reviews</full-title><abbr-1>Endocr Rev</abbr-1></alt-periodical><pages>404-433</pages><volume>18</volume><dates><year>1997</year></dates><isbn>ISSN 0163-769X
EISSN 0163769X</isbn><label>16513</label><urls></urls></record></Cite></EndNote>], assuming that the variation in fT4 was due to the corresponding changes in hCG. An empirical relationship for changes in **VMAXNISF_THY_I** with gestational age based on variation in radio-iodide uptake was included separately in the model, based on [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Clewell</Author><Year>2007</Year><RecNum>1828</RecNum><IDText>756734</IDText><DisplayText>Clewell et al. (2007)</DisplayText><record><rec-number>1828</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">1828</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Clewell, R. A.</author><author>Merrill, E. A.</author><author>Gearhart, J. M.</author><author>Robinson, P. J.</author><author>Sterner, T. R.</author><author>Mattie, D. R.</author><author>Clewell, H. J.</author></authors></contributors><titles><title>Perchlorate and radioiodide kinetics across life stages in the human: using PBPK models to predict dosimetry and thyroid inhibition and sensitive subpopulations based on developmental stage</title><secondary-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</secondary-title><alt-title>J Toxicol Environ Health A</alt-title><short-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</short-title></titles><periodical><full-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</full-title><abbr-1>J Toxicol Environ Health A</abbr-1></periodical><alt-periodical><full-title>Journal of Toxicology and

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Environmental Health, Part A: Current Issues</full-title><abbr-1>J Toxicol Environ Health A</abbr-1></alt-periodical><pages>408-428</pages><volume>70</volume><number>5</number><dates><year>2007</year></dates><isbn>ISSN 1528-7394
EISSN 1087-2620</isbn><label>756734</label><urls><related-urls><url>http://dx.doi.org/10.1080/15287390600755216</url></related-urls></urls><electronic-resource-num>10.1080/15287390600755216</electronic-resource-num><language>English</language></record></Cite></EndNote>], although it might otherwise be presumed that hCG stimulates both NIS expression and TH production. Therefore, the direct functional application of hCG stimulation was only applied to T4 and T3 production: both were assumed to increase in proportion to the serum concentration of hCG, with **KHCG** being the proportionality constant. Considering that only 10 time-matched values of fT4 and hCG were used to estimate **KHCG** (Figure A-42) the uncertainty in its value might be considered high. However, comparison of 1T model predictions to TH changes during pregnancy show that the resulting model recapitulates the observed increases in total T4 and total T3 up to GW 16 fairly well (Figure A-57 and Figure A-58). Removing either the two highest hCG or 4 highest hCG points from Figure A-42 and revising the regression yields a range of slopes from 0.0038-0.0059 (ng/dL)/(kIU/L). Dividing this range by twice the slope obtained with all data included yields an uncertainty factor of 0.26, which will be used for this analysis.

Since **KHCG** multiplies the empirical curve fitted to the observed median hCG vs. GW from [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Korevaar</Author><Year>2015</Year><RecNum>2397</RecNum><IDText>3755222</IDText><DisplayText>Korevaar et al. (2015)</DisplayText><record><rec-number>2397</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2397</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, T. I.</author><author>Steegers, E. A.</author><author>de Rijke, Y. B.</author><author>Schalekamp-Timmermans, S.</author><author>Visser, W. E.</author><author>Hofman, A.</author><author>Jaddoe, V. W.</author><author>Tiemeier, H.</author><author>Visser, T. J.</author><author>Medici, M.</author><author>Peeters, R. P.</author></authors></contributors><titles><title>Reference ranges and determinants of total hCG levels during pregnancy: The Generation R Study</title><secondary-title>European Journal of Epidemiology</secondary-title><alt-title>Eur J Epidemiol</alt-title><short-title>European Journal of Epidemiology</short-title></titles><periodical><full-title>European Journal of Epidemiology</full-title><abbr-1>Eur J Epidemiol</abbr-1></periodical><alt-periodical><full-title>European Journal of Epidemiology</full-title><abbr-1>Eur J Epidemiol</abbr-1></alt-periodical><pages>1057-1066</pages><volume>30</volume><number>9</number><dates><year>2015</year></dates><isbn>ISSN 0393-2990
EISSN 1573-7284</isbn><label>3755222</label><urls><related-urls><url>http://dx.doi.org/10.1007/s10654-015-0039-0</url></related-urls></urls><electronic-resource-num>10.1007/s10654-015-0039-0</electronic-resource-num><language>English</language></record></Cite></EndNote>], the variability and potential

uncertainty in that curve and data should also be considered. [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Korevaar</Author><Year>2015</Year><RecNum>2397</RecNum><IDText>3755222</IDText><DisplayText>Korevaar et al. (2015)</DisplayText><record><rec-number>2397</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">2397</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, T. I.</author><author>Steegers, E. A.</author><author>de Rijke, Y. B.</author><author>Schalekamp-Timmermans, S.</author><author>Visser, W. E.</author><author>Hofman, A.</author><author>Jaddoe, V. W.</author><author>Tiemeier, H.</author><author>Visser, T. J.</author><author>Medici, M.</author><author>Peeters, R. P.</author></authors></contributors><titles><title>Reference ranges and determinants of total hCG levels during pregnancy: The Generation R Study</title><secondary-title>European Journal of Epidemiology</secondary-title><alt-title>Eur J Epidemiol</alt-title><short-title>European Journal of Epidemiology</short-title></titles><periodical><full-title>European Journal of Epidemiology</full-title><abbr-1>Eur J Epidemiol</abbr-1></periodical><alt-periodical><full-title>European Journal of Epidemiology</full-title><abbr-1>Eur J Epidemiol</abbr-1></alt-periodical><pages>1057-1066</pages><volume>30</volume><number>9</number><dates><year>2015</year></dates><isbn>ISSN 0393-2990
EISSN 1573-7284</isbn><label>3755222</label><urls><related-urls><url>http://dx.doi.org/10.1007/s10654-015-0039-0</url></related-urls></urls><electronic-resource-num>10.1007/s10654-015-0039-0</electronic-resource-num><language>English</language></record></Cite></EndNote>] is one component of the larger Generation R study conducted in the Netherlands [ADDIN EN.CITE <EndNote><Cite AuthorYear="1"><Author>Jaddoe</Author><Year>2012</Year><RecNum>3015</RecNum><IDText>3116363</IDText><DisplayText>Jaddoe et al. (2012)</DisplayText><record><rec-number>3015</rec-number><foreign-keys><key app="EN" db-id="frats9st8vppzsexzdk5aep4zvt0t9pd2ser" timestamp="1501191018">3015</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Jaddoe, V. W.</author><author>van Duijn, C. M.</author><author>Franco, O. H.</author><author>van der Heijden, A. J.</author><author>van Iizendoorn, M. H.</author><author>de Jongste, J. C.</author><author>van der Lugt, A.</author><author>Mackenbach, J. P.</author><author>Moll, H. A.</author><author>Raat, H.</author><author>Rivadeneira, F.</author><author>Steegers, E. A.</author><author>Tiemeier, H.</author><author>Uitterlinden, A. G.</author><author>Verhulst, F. C.</author><author>Hofman, A.</author></authors></contributors><titles><title>The Generation R Study: design and cohort update 2012</title><secondary-title>European Journal of Epidemiology</secondary-title><alt-title>Eur J Epidemiol</alt-title><short-title>European Journal of Epidemiology</short-title></titles><periodical><full-title>European Journal of Epidemiology</full-title><abbr-1>Eur J Epidemiol</abbr-1></periodical><alt-periodical><full-title>European Journal of

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Epidemiology</full-title><abbr-1>Eur J Epidemiol</abbr-1></alt-periodical><pages>739-756</pages><volume>27</volume><number>9</number><dates><year>2012</year></dates><isbn>ISSN 0393-2990
EISSN 1573-7284</isbn><label>3116363</label><urls><related-urls><url>http://dx.doi.org/10.1007/s10654-012-9735-1</url></related-urls></urls><electronic-resource-num>10.1007/s10654-012-9735-1</electronic-resource-num><language>English</language></record></Cite></EndNote>], with samples taken from nearly 8200 pregnant women. It is judged to be a high quality study, and the sample size is sufficient to accurately identify the population median. That it is not a U.S. population introduces some uncertainty, but considering that TH data from a number of countries are shown in Figure A-57 and Figure A-58 to be largely consistent, this additional uncertainty is also considered limited. Hence the uncertainty in the empirical curve for median hCG with gestation is considered low. However, using the data for 2.5th, median, and 97.5th percentiles of hCG in Figure A-41, an average variability factor for hCG levels in the pregnant population is 0.85, and is used to represent variability for **KHCG.**

[ADDIN EN.REFLIST]

ED_005043_00079896-00018

Message

From: Evalenko, Sandy [Evalenko.Sandy@epa.gov]
Sent: 5/26/2020 7:27:04 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Time sensitive-Quick Question: Action for OMB review: NPDWR: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule.20200526.docx

FYI--

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Tuesday, May 26, 2020 3:14 PM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Subject: RE: Time sensitive-Quick Question: Action for OMB review: NPDWR: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Importance: High

Please call me at Ex. 6 Personal Privacy (PP)

From: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Sent: Tuesday, May 26, 2020 3:02 PM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Subject: Time sensitive-Quick Question: Action for OMB review: NPDWR: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Importance: High

OP called and Perchlorate is moving through OP for clearance to go to OMB; however, Mary Manibusan called after talking with Bill Nickerson to see why we didn't include EO 12866. I explained that this is just a notice and not a rulemaking. Even though this is a notice; we will want to include EO 12866 because it's going to OMB and is very visible. OP wants it in the FRN before it goes to OMB and think that OMB will want to see it. FYI – OWM adds EO 12866 in notices for general permits when they go to OMB for EO reviews. I know that you all are swamped so I cut and pasted Template B for EO 12866 at page 38. Please review and let me know if you want any edits to the 2-3 sentences that I'm recommending to add.

Can you all get back to me today?

Sandy

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

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

Thanks,
Sandy

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

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

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

---

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

Hi Charlotte,

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

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

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

Attachments

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

Thank you,
Janita

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

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

Sam,

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

Pooja

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

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

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

Pooja

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

Message

From: Gilbert, Mary E. [Gilbert.Mary@epa.gov]
Sent: 3/27/2017 2:02:42 PM
To: Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]
CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]
Subject: RE: BBDR Model Status: a surprising result, but maybe shouldn't be
Attachments: Gilbert et al Toxicology 2011.pdf

HI Paul and Jeff

I have read through Jeff's comments and agree with Jeff's calls on what you have done Paul. Clearly a lot of work and thinking went into your proposals!

I have only a couple of comments to add to Jeff's and added them below in purple font....

Ex. 6 Personal Privacy (PP) will hopefully have access to email. I will respond when I can

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

From: Fisher, Jeffrey [mailto:Jeffrey.Fisher@fda.hhs.gov]
Sent: Saturday, March 25, 2017 8:00 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; kinetics@leavens.us; Miller, Gregory <Miller.Gregory@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>
Cc: Noyes, Pamela <Noyes.Pamela@epa.gov>; Cantilli, Robert <Cantilli.Robert@epa.gov>; Gilbert, Mary E. <Gilbert.Mary@epa.gov>
Subject: RE: BBDR Model Status: a surprising result, but maybe shouldn't be

Good Morning Paul and others,
See comments below.

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, March 24, 2017 8:35 AM
To: Olson, Daniel; Christ, Lisa; Flowers, Lynn; Hafez, Ahmed; Helm, Erik; Fisher, Jeffrey; kinetics@leavens.us; Miller, Gregory; Strong, Jamie; Kapraun, Dustin; Georges, Jessica
Cc: Noyes, Pamela; Cantilli, Robert; Gilbert, Mary E.
Subject: BBDR Model Status: a surprising result, but maybe shouldn't be

Perchlorate team,

This is a bit of a long email, but I'm asking in particular that Jeff and Mary read through, and address the highlighted question at the end.

I was preparing to show the impact of my first pass at TSH feedback, and so I wanted to first create a plot without the feedback (baseline model) to show the contrast.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Message

From: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Sent: 5/21/2020 12:35:01 PM
To: Parikh, Pooja [Parikh.Pooja@epa.gov]
CC: Wehling, Carrie [Wehling.Carrie@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: RE: Request for Concurrence - Revised Perchlorate FRN
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20200521.docx

Thanks Pooja,

I have made the revisions in the attached file. Can you send an email indicating that OGC concurs with this version? We need the email to include it in the record and to allow OW to move the document forward.

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Wednesday, May 20, 2020 8:16 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: RE: Request for Concurrence - Revised Perchlorate FRN

Hi Sam

I've reviewed the changes in the redline version; had only one small tweak to the language on page 6 (and caught a couple of extra commas on page 9). Please see attached. Thanks.

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, May 20, 2020 4:23 PM

To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: Request for Concurrence - Revised Perchlorate FRN

Hi Pooja,

We were asked by OW to get OGC's concurrence on the latest version of the FRN before it gets transmitted to OP.

Here I am attaching a redline version that captures the latest changes that we made to the notice since Eric had discussions with OGC. Let me know if you have any questions.

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

"USEPA Protecting Human Health and the Environment"

Appointment

From: Olson, Daniel [Olson.Daniel@epa.gov]
Sent: 2/14/2017 6:22:57 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]

Subject: BBDR Model Status
Attachments: Perchlorate Peer Review Report_TO 2015-22_Draft.docx; NHANES Prelim Report Summary.docx
Location: 2400 east; Ex. 6 Personal Privacy (PP)

Start: 2/14/2017 8:00:00 PM
End: 2/14/2017 9:00:00 PM
Show Time As: Tentative

Recurrence: Weekly
every Tuesday from 3:00 PM to 4:00 PM

Room change to 2400 east.

Attached please find:

1. Draft peer review report. We just received and have not had the opportunity to review. Consider this a close hold until we review and discuss internally.
2. A write up of the additional three NHANES correlation runs -
   - Since TSH levels in pregnant and non-pregnant women are statistically the same, run a combined set of correlations for TSH
   - Run a correlation between fT4 and TSH in pregnant women
   - Combine data on urinary perchlorate, nitrate and thiocyanate for pregnant and non-pregnant women and evaluate for correlation in these combined data

Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 7/16/2019 3:31:18 PM
To: Miller, Gregory [Miller.Gregory@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Strong, Jamie [Strong.Jamie@epa.gov]; Lan, Alexis [lan.alexis@epa.gov]
Subject: RE: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints
Attachments: EST_AEP_manuscript_STiCS FINAL_OGWDW.docx

Hi Greg,
I had a few small edits and one comment. Please see attached.

Thanks,
Lisa

From: Miller, Gregory
Sent: Friday, July 12, 2019 11:13 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Strong, Jamie <Strong.Jamie@epa.gov>
Subject: FW: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Lisa & Sam,
Sorry I didn't get this to you a few days ago, but I just realized that this is the same perchorlate manuscript that we've already reviewed 2 times previously. Apparently the journal rejected the anonymized perchlorate version that we last reviewed, so they've added the perchlorate detail back in. Please take another look and flag any concerns you might have.

Thanks!

Greg Miller, Senior Environmental Health Scientist
Team Lead, Human Health Risk Assessment Branch
Office of Science and Technology, Health and Ecological Criteria Division
US Environmental Protection Agency, Office of Water
1200 Pennsylvania Ave, NW (MC 4304T)
Washington, DC 20460

phone: (202) 566-2310

From: Strong, Jamie
Sent: Tuesday, July 9, 2019 12:54 PM
To: Miller, Gregory <Miller.Gregory@epa.gov>
Cc: Soares, Barbara <soares.barbara@epa.gov>
Subject: FW: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Can you review this Greg?

From: Ow Pub Tracker <OwPubTracker@cadmusgroup.com>
Sent: Tuesday, July 09, 2019 12:50 PM
To: Strong, Jamie <Strong.Jamie@epa.gov>
Cc: Behl, Betsy <Behl.Betsy@epa.gov>; Soares, Barbara <soares.barbara@epa.gov>; Ow Pub Tracker <OwPubTracker@cadmusgroup.com>; Reiley, Mary <Reiley.Mary@epa.gov>; Brady, Catherine <brady.catherine@epa.gov>
Subject: Due 7/23/19, Advanced Notice Review for Hines - A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Hi Jamie,

OW received the attached manuscript: **Hines – A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks** and OW Transmittal Form from ORD for Advanced Notice Review. The subject matter of the manuscript most closely aligns with the work of OST. Mary and Catherine will be coordinating the review of the manuscript across OST and with the other NWP Research POCs. Please send your comments to Mary, Catherine, and Cadmus no later **Tuesday, July 23**. We will send a reminder two days before the review is due. Mary will forward the review to Ed Ohanian and Owen McDonough for clearance and then return the cleared review to ORD.

Please include Mary, Catherine, and Cadmus on correspondence regarding this review so that the spreadsheet tracking the manuscript reviews can be kept current. Please contact Cadmus and cc Mary and Catherine if you have questions or delays.

Thanks,

Alex Taylor | Research Analyst
The Cadmus Group LLC
3100 Clarendon Blvd, Suite 400 | Arlington, VA 22201
(703) 247-6144

From: Brady, Catherine <brady.catherine@epa.gov>
Sent: Tuesday, July 9, 2019 8:54 AM
To: Ow Pub Tracker <OwPubTracker@cadmusgroup.com>
Cc: Reiley, Mary <Reiley.Mary@epa.gov>
Subject: [EXT] FW: Deadline July 24th -- Round 2 ADVANCE NOTIFICATION - ORD-027781 Hines et al. A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Good Morning Cadmus,

Attached is a new manuscript with fact sheets and supplemental information. The correct transmittal will be sent to you later today, hopefully. In the meantime could you please send this to the POCs, OST should be the lead office for this document. Thank you!

Catherine Brady
ORISE Participant
Health & Ecological Criteria Division
U.S. EPA| Office of Water|Office of Science & Technology

From: Bahadori, Tina
Sent: Tuesday, July 9, 2019 2:00 AM
To: Reiley, Mary <Reiley.Mary@epa.gov>; Brady, Catherine <brady.catherine@epa.gov>
Cc: Ohanian, Edward <Ohanian.Edward@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Fleming, Megan

<Fleming.Megan@epa.gov>; VanDrunick, Suzanne <vanDrunick.Suzanne@epa.gov>
Subject: Deadline July 24th -- Round 2 ADVANCE NOTIFICATION - ORD-027781 Hines et al. A Quantitative AEP/AOP Case Study Integrating Ecological and Human Health Endpoints

Dear OW Colleagues,

Attached for your policy review, please find the newest version of a manuscript authored by ORD's David Hines and his coauthors entitled, "A quantitative source-to-outcome case study to demonstrate the integration of human health and ecological endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks."

Ex. 5 Deliberative Process (DP)

For your convenience, in addition to the revised manuscript, a file of supportive or supplemental information, an ORD fact/impact sheet, and an OW transmittal form have been attached eh **If as you review the this paper, you run across any policy show-stoppers please let me know by no later than Wednesday, July 24th.**

I look forward to hearing back from you. Please let me know if you need additional information.

With warm regards,

Tina

==========

Tina Bahadori, Sc.D.
Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

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Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 4/6/2020 12:30:15 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN
Attachments: Draft Perchlorate Reg Det Withdrawal FR Notice 4-2-20 v1 Redline-lc.docx

Hi Sam,
I had a few edits, typos, clarifying language in the attached. Please make these edits and send the clean version to Eric with a cc to me. I'm lokking over the memos quickly tis morning too.

Thanks so much!
Lisa

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Thursday, April 02, 2020 5:31 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Newcamp, Caitlin <Newcamp.Caitlin@epa.gov>; Alattar, Zaineb <alattar.zaineb@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN

Hi Eric

We have incorporated most of your edits as well as the new items discussed during our meeting on Tuesday.

Ex. 5 Deliberative Process (DP)

In addition, here you will see the memos that the team prepared for transmitting the package up the review/concurrence chain. Please let me know if you have further comments or any questions regarding the attached documents.

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

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Saturday, March 28, 2020 11:08 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: Deliberative Draft - Perchlorate Reg Det Withdrawal FRN

Sam:
Thank you for preparing the draft final action for perchlorate. I have reviewed the document and have a number of edits and comments in the attached. Please let me know if you would like to arrange a meeting to discuss my comments.
Thank you again for the work you and the team have done in these challenging conditions.

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, March 20, 2020 2:00 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: Draft - Perchlorate Reg Det Withdrawal FRN

Hi Eric,

Attached you will find the draft FRN announcing the withdrawal of the Reg Det for perchlorate. Lisa already reviewed an earlier version of this notice and we have incorporated the requested edits. We also sent this version of the FRN to OGC for their review and feedback.

We will work on incorporating your comments and input concurrently with any input we get from OGC.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 11/8/2016 3:54:34 PM
To: Perkinson, Russ [Perkinson.Russ@epa.gov]
Subject: FW: summarizing - final who is doing what on charge...and report and code and Annie's paper
Attachments: BBDR SAB Charge_References.docx

From: Noyes, Pamela
Sent: Tuesday, November 08, 2016 10:40 AM
To: Flowers, Lynn <Flowers.Lynn@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>
Cc: Schlosser, Paul <Schlosser.Paul@epa.gov>; Cantilli, Robert <Cantilli.Robert@epa.gov>; Fegley, Robert <Fegley.Robert@epa.gov>
Subject: RE: summarizing - final who is doing what on charge...and report and code and Annie's paper

Hi Lisa,
Attached is the list of references to be added to the charge.
Thanks,
Pam

Pamela D. Noyes, PhD
U.S. Environmental Protection Agency
Office of Science Coordination and Policy (OSCP)
Endocrine Disruptor Screening Progam
1200 Pennsylvania Ave, NW (7203M)
Washington, DC 20460

Office: 202-564-3043
Fax: 202-564-8482

From: Flowers, Lynn
Sent: Monday, November 07, 2016 11:36 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>
Cc: Noyes, Pamela <Noyes.Pamela@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Cantilli, Robert <Cantilli.Robert@epa.gov>; Fegley, Robert <Fegley.Robert@epa.gov>
Subject: summarizing - final who is doing what on charge...and report and code and Annie's paper

Charge-

1) OW has the pen back!
2) change the first mention of BBDR in the charge
3) after the meeting we discussed re-looking at 1 c in the charge – just to be sure of language, but we are OK. No changes.
4) reference list for charge – **Pam will do this and send to you**
5) after the meeting we discussed re-ordering the questions – but we are OK. Don't do it…

AWWA and Intertox comments –
I am sure you know what to say, but I wrote down ORDs comments on these charge questions in an email on Friday (Nov 4) – it is short.

Ex. 5 Deliberative Process (DP)

That's all I've got!

Lynn Flowers, PhD, DABT
Office of Science Policy
US EPA
Washington, DC
202-564-6293

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 9/17/2018 7:07:19 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints
Attachments: EST_AEP_manuscript_v1 OW_OST.DOCX; ORD_027781 Hines OW Transmittal Form OW_OST.DOCX; EST_AEP_manuscript_v1 OW_OST.lc.DOCX

My comments attached.

From: Huff, Lisa
Sent: Thursday, September 13, 2018 3:09 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints

Sam,
Please review the attached manuscript and provide comments to Lisa and I if possible by COB Monday. That will give us time to discuss with OST before sending them on by the due date 9/19. Jamie also attached Greg's comments for your information.

Thanks,

Lisa Foersom Huff

Associate Branch Chief
Targeting and Analysis Branch
Standards and Risk Management Division
Office of Groundwater and Drinking Water
U.S. EPA
EPA East Bldg. Rm. 2357 H
202-566-0787

From: Burneson, Eric
Sent: Thursday, September 13, 2018 2:28 PM
To: Huff, Lisa <Huff.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: Fwd: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints

Please review and let us know if you have concerns.

Sent from my iPhone

Begin forwarded message:

From: "Strong, Jamie" <Strong.Jamie@epa.gov>
Date: September 13, 2018 at 2:11:59 PM EDT
To: "Behl, Betsy" <Behl.Betsy@epa.gov>
Cc: "Burneson, Eric" <Burneson.Eric@epa.gov>, "Christ, Lisa" <Christ.Lisa@epa.gov>
Subject: FW: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints

Betsy,
We have serious concerns related to this paper submitted for review by ORD. It has significant implications for perchlorate. I am attaching Greg's comments and including OGWDW here for awareness. I think that this paper has significant policy issues.

Let me know when we can talk.

Thanks,
Jamie

From: Miller, Gregory
Sent: Tuesday, September 11, 2018 1:12 PM
To: Strong, Jamie <Strong.Jamie@epa.gov>
Subject: FW: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints
Importance: High

Here are my comments. I wanted you to have a chance to review them before we send them up. Sam in OGWDW has committed to reviewing the manuscript as well. We should share comments with him after you have a look.

Greg

From: Soares, Barbara
Sent: Thursday, September 6, 2018 8:27 AM
To: Miller, Gregory <Miller.Gregory@epa.gov>
Cc: Rogers, Emily <rogers.emily@epa.gov>
Subject: Fw: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints
Importance: High

Greg,

Would a review of this manuscript by 9/13-9/14 be possible?

Thank you,

Barbara

From: Reiley, Mary
Sent: Thursday, September 6, 2018 7:55 AM
To: Behl, Betsy
Cc: Balasa, Kate; Braverman, Carole; Corona, Joel; Emerson, Vanessa; Lowenstein, Zachary; Metchis, Karen; Ohanian, Edward; Reiley, Mary; Rogers, Emily; Smith, Bernicel; Smith, Lameka; Soares, Barbara; Trombley, Michael; Tucker, Nicole; Zahreddine, Phil
Subject: Due 9/19/18: ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints

Good morning:

OST/HECD is the lead reviewer for this manuscript. Betsy, please let me know who on your staff will conduct the review.

POC's if your offices have comments, please send them to me by 9/19. I will compile and forward via Ed to OW-IO on 9/20.

Thank you!

Mary

From: Ohanian, Edward
Sent: Wednesday, September 05, 2018 5:43 PM
To: Reiley, Mary <Reiley.Mary@epa.gov>
Subject: Deadline 9/20/2018 ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints

Hi Mary,
The lead office to conduct this review is OST/HECD. The other POCs need to also send their comments to you (HECD). Thx. Ed

Edward V. Ohanian, Ph.D.
Associate Director for Science
USEPA/Office of Water (MC: 4301T)
(202) 566-1117 (Voice)
(202) 566-0441(Fax)

Mailing Address:
U.S. Environmental Protection Agency
Rm: 5231P/Q WJC East (MC: 4301T)
1200 Pennsylvania Avenue, NW

Washington, DC 20460

Address for Visitors and Deliveries:
1201 Constitution Avenue, NW
WJC East, 5th Floor, Rm: 5231P/Q
Washington, DC 20004

From: Bahadori, Tina
Sent: Wednesday, September 05, 2018 5:20 PM
To: Ohanian, Edward <Ohanian.Edward@epa.gov>
Cc: Fleming, Megan <Fleming.Megan@epa.gov>; Champlin, Anna <Champlin.Anna@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; vanDrunick, Suzanne <vanDrunick.Suzanne@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: Deadline 9/20/2018 ADVANCED NOTIFICATION - ORD-027781 Hines et al. A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints

Dear Ed,

A multidisciplinary team in HHRA has produced a manuscript entitled, "A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological Endpoints using the Aggregate Exposure Pathway and Adverse Outcome Pathway frameworks." This work expands a previous case study, which focused on integration of toxicity mechanisms using the Adverse Outcome Pathway (AOP) for a data rich chemical (perchlorate anion, ClO_4^-), and suggested linking this toxicity data to a hypothetical exposure model to demonstrate a quantitative source-to-outcome approach. The authors quantitatively describe external exposure under three different hypothetical contamination scenarios for humans, small mammals, and fish using Monte Carlo simulations to describe exposure distributions. They applied previously published, species-specific Physiologically Based Pharmacokinetic (PBPK) models to link external exposure predictions to internal exposure ranges in these three groups of organisms, and demonstrate how these predictions, along with the integrated AEP and AOP frameworks, can inform a comprehensive source-to-outcome approach to cumulative risk assessment that integrates human health and ecological endpoints. The case study presented in this work was able to: 1) predict environmental concentrations and external exposure in multiple species at a hypothetical site; 2) quantify species-specific relative source contribution under different illustrative exposure scenarios; 3) demonstrate the linkage between external exposures, internal doses (target site exposures), and mechanistic toxicity endpoints; 4) highlight how the joint AEP-AOP construct can identify data gaps along a source-to-outcome continuum; and 5) provide an example of how the AEP-AOP approach can help to quantify uncertainties in risk predictions. Importantly, this work was conducted for a hypothetical ecosystem and is not a risk assessment for the focal chemical. Therefore, there are no direct implications of this work for regulation of the chemical or organisms included in the demonstrative case study.

Given OW's interest in cumulative risk assessment and the use of perchlorate as the case study, we wanted to bring this manuscript to your attention and ask that you review it for potential policy implications to your office. **If as you review the this paper, you run across any show-stoppers please let me know by no later than Thursday, September 20, 2018.**

To facilitate review, in addition to the manuscript, a one-page manuscript information sheet is also attached. The manuscript is targeted for submission to *Environmental Science and Technology*.

I look forward to hearing back from you. Please let me know if you need additional information.

With warm regards,

Tina

==========

Tina Bahadori, Sc.D.
Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 12/11/2017 2:05:17 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: FW: BBDR comments
Attachments: WA459_T3_Public Comments for BBDR_171206.xlsx

Hi Sam,
I reviewed the attached matrix and did not have comments or questions. Please work with Lynn Flowers to coordinate ORD input.

Thanks,
Lisa

From: Hafez, Ahmed
Sent: Thursday, December 07, 2017 6:59 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: BBDR comments

Morning Lisa and Sam,

Attached is the comment matrix for the BBDR model public comments. We have **bolded** the comments we think are important and would like ORD input on. We've also underlined the pertinent parts of the comments for ease of reading.

A comment matrix for the MCLG approaches is also being finalized and I'll pass that along when complete.

Let me know if you have any questions.

Thanks,
Ahmed

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

"The person you are the most afraid to contradict is yourself."
--N. N. Taleb

From: Lauren Brown [mailto:Lauren_Brown@abtassoc.com]
Sent: Wednesday, December 06, 2017 3:37 PM
To: Hafez, Ahmed <Hafez.Ahmed@epa.gov>
Cc: Lawrence Reichle <Lawrence_Reichle@abtassoc.com>; Ryan Klein <Ryan_Klein@abtassoc.com>
Subject: BBDR comments

Hi Ahmed:
Attached is the comment matrix we have pulled together for ORD. It includes all the comments we received related to the BBDR model. We've reviewed and **bolded** those that we believe are most important, though I think it would be best if ORD reviewed them all since they have a better understanding of the model and the implications of some of the comments. We have also taken your approach of trying to underline the most important part of the comment to help the reader.

In this matrix we have a "general topic" column which, for this spreadsheet, should almost all be the BBDR model as these were pulled from the larger matrix. We then have the "specific" topic area where one can drill down into the different areas that comments were received on. If you sort alphabetically by this column you should be able to easily group comments which are similar. We also kept in a column of some of our initial thoughts on some of the comments. These only pertain to comments for which we had quick initial responses to – this is has not been done systematically throughout the matrix.

Please let us know if you have questions on this.

Lauren

Lauren Brown | Associate/Scientist | Abt Associates
O: 301.347.5832 | F: 301.828.9859 | www.abtassociates.com

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BOLD THINKERS DRIVING REAL-WORLD IMPACT

This message may contain privileged and confidential information intended solely for the addressee. Please do not read, disseminate or copy it unless you are the intended recipient. If this message has been received in error, we kindly ask that you notify the sender immediately by return email and delete all copies of the message from your system.

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 10/5/2017 3:02:58 PM
To: Hafez, Ahmed [Hafez.Ahmed@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: Perchlorate Charge Question - question about Lisa's email discussion below
Attachments: OMB SBA response.docx

Can you please take a look at what I've drafted so far to reply back to Jim and Kevin?

Thanks
Lisa

From: Hafez, Ahmed
Sent: Thursday, October 05, 2017 6:22 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate Charge Question - question about Lisa's email discussion below

Hi Lisa,

I'm having Abt craft a more thorough/complete explanation that will hopefully make things more obvious as to why the studies were not included.

I would hold off on what I sent earlier.

Thanks,
Ahmed

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

"It is better to do things that you cannot explain, than to explain things that you cannot do."
--Nassim Taleb

From: Bromberg, Kevin L. [mailto:kevin.bromberg@sba.gov]
Sent: Wednesday, October 04, 2017 5:20 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>
Cc: James_H_Kim@ Ex. 6 Personal Privacy (PP) Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Perchlorate Charge Question - question about Lisa's email discussion below

Lisa, I am confused by your statement in the last paragraph that neither Casey nor CATS did investigate cognitive outcomes. Both CATs and Casey – both large studies - studied cognitive outcome for offspring of mothers with hypothyroxinemia – see two paragraphs below from the Casey 2017 study. Why did your note indicate otherwise? Why aren't studies of treatment to normal hormone levels relevant to this evaluation of neurodevelopmental effects? Thanks for the Cooper and Pearce article, which does raise some issues. (All studies have

issues!) I think these studies should be added to the report in some abbreviated form, at a minimum to the Group 1 reports (quantitative analysis of ft4).

http://www.nejm.org/doi/full/10.1056/NEJMoa1606205#t=articleResults Casey Study

> The results of our trials are consistent with those of the CATS study, which was a thyroid-screening trial involving 21,846 pregnant women, primarily from the United Kingdom. Women in that trial were either screened immediately and treated with levothyroxine if they were identified as having subclinical hypothyroidism or hypothyroxinemia or had their serum frozen to be analyzed on completion of the pregnancy. **The results of IQ testing of the children at 3 years of age did not differ significantly between children whose mothers had been immediately treated during the pregnancy and those whose mothers had treatment that was deferred.** Thyroid hormone–replacement therapy in the CATS study was initiated at a median gestational age of 13 weeks 3 days, as compared with 16 weeks 4 days and 18 weeks in our two trials.[17] However, 24% of the children in the CATS study were lost to follow-up. In the current trials, the follow-up rate at 5 years of age was more than 92%.
>
> Several studies have also suggested that either a high maternal thyrotropin level or hypothyroxinemia is associated with externalizing behavioral problems such as attention deficit–hyperactivity disorder (ADHD).[25,26] In the Generation R Study, 8-year-old children of women from an iodine-deficient geographic area who had been identified with hypothyroxinemia before 20 weeks of gestation were found to have higher ADHD index scores than children of women without hypothyroxinemia.[26] This association persisted after adjustment for IQ. **We did not identify any significant between-group differences in ADHD index scores in either of our trials, and the scores were well within the normal range. Moreover, the Child Behavior Checklist scores did not reveal any evidence of behavioral problems in children whose mothers with subclinical hypothyroidism or hypothyroxinemia were in the placebo group. The CATS study also did not detect any behavioral improvements in children who had been exposed to thyroid hormone replacement.**[17]

From: Christ, Lisa [mailto:Christ.Lisa@epa.gov]
Sent: Wednesday, October 04, 2017 11:56 AM
To: Bromberg, Kevin L.; Burneson, Eric; Hafez, Ahmed
Cc: James_H_Kim(Ex. 6 Personal Privacy (PP) Hernandez-Quinones, Samuel
Subject: RE: Perchlorate Charge Question - My latest thoughts - feel free to modify

Kevin,
Thank you for the additional input on the charge. Also, I have summarized the discussion from yesterday.

You asked: Why do you see less affect (change in fT4 or change in IQ) at the 2.5th percentile than at the 50th percentile? Intuitively you would expect to see a greater affect when the mother has very low fT4, however, the affect is greater at the 50th percentile.

Response: Report tables 24, 30, 31, 32 and 33 provide results from studies by Finken, Pop and Vermiglio.

To develop these tables, EPA used the BBDR model output for the gestation week (12,13,16) that corresponds to the GW used in each study. Therefore, the BBDR predicted fT4 value at a zero dose of perchlorate differ.

The BBDR model output is the central tendency (i.e., 50th percentile). EPA created the distribution around the 50Th percentile BBDR model output as described in Chapter 4 of the report.

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. Additional details on uncertainties can be found in section 6.5.6 of the report.

Also, we did receive and evaluate the studies you provided. Casey and the Lazarus (CATS) studies did not investigate the effects of hypothyroximemia on cognitive outcome. They looked at kids born to women who were at 'low end of normal' thyroid function and who were either given or not given levothyroxine. There was no comparison to developmental outcome in children born to women with 'optimal' hormone levels. We also reviewed the Cooper and Pearce, 2017 paper which provided additional perspectives. http://www.sempr.org.br/files/1023/Beneficio_do_tratamento_do_hiposubclinico_na_gestacao_Editor%20ial_NEJM%202017.pdf

Best,

Lisa

From: Bromberg, Kevin L. [mailto:kevin.bromberg@sba.gov]
Sent: Wednesday, October 04, 2017 11:33 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: James_H_Kim Ex. 6 Personal Privacy (PP)
Subject: Perchlorate Charge Question - My latest thoughts - feel free to modify

Thanks for that thoughtful conversation yesterday.

Lisa and I just talked – and not I'm memorializing my latest thoughts.

The apparent discrepancy with regard to increase in neurodevelopmental outcome is due potentially to two factors – the distribution of ft4 about the median AND the regression equations. We should not
Focus on on just the distribution of ft4 levels, as I thought earlier.

A better home for these thoughts would be in Charge Question 11, rather than Charge Question 13. See italicized additions.

11. EPA used regression analyses to predict the magnitude of change in each of the neurodevelopmental endpoints given a change in fT4 as a result of increased perchlorate exposure at different iodide intakes. *In Tables 24, 25 ...and 33, EPA presents the predicted size of these changes. These effects are projected to be greater for the median fT4 in comparison to the lower fT4s, which is not the expected result. This is a function of the assumed distribution about the median (see charge question 13) and the regression equations derived for each study.*
    a. Please comment on the assumptions, strengths, and limitations of using the regression analyses to inform the relationship between thyroid hormone levels and neurodevelopmental outcomes.
    b. Please identify additional data or analyses EPA could use to quantify the relationship between thyroid hormone levels and neurodevelopmental effects, including how this information would be expected to improve the analysis.
    c. Please comment on whether there is a magnitude of change in fT4 below which the relationship between fT4 and neurodevelopmental effects should not be used because it is too uncertain.

d. Please comment on whether other studies that were identified in the literature search (e.g., studies that found effects but lacked statistical significance, studies that did not find an effect, studies that found categorical relationships between fT4 and neurodevelopmental outcomes) could be utilized to quantitatively characterize the relationship between fT4 and neurodevelopmental outcomes or inform uncertainty associated with the analysis presented.

Kevin Bromberg
Assistant Chief Counsel for Environmental Policy
SBA // Office of Advocacy
409 3rd St. SW, Washington, D.C. 20416
kevin.bromberg@sba.gov 202.481.2963
202.205.6964

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 10/5/2017 12:02:49 PM
To: Hafez, Ahmed [Hafez.Ahmed@epa.gov]
CC: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: Perchlorate Charge Question - question about Lisa's email discussion below

Thanks Ahmed! let's respond to all the questions in one email. I'll wait until you have input from Abt.

From: Hafez, Ahmed
Sent: Thursday, October 05, 2017 6:22 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate Charge Question - question about Lisa's email discussion below

Hi Lisa,

I'm having Abt craft a more thorough/complete explanation that will hopefully make things more obvious as to why the studies were not included.

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Thanks,
Ahmed

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

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From: Bromberg, Kevin L. [mailto:kevin.bromberg@sba.gov]
Sent: Wednesday, October 04, 2017 5:20 PM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>
Cc: James_H_Kim@ Ex. 6 Personal Privacy (PP) Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
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From: Christ, Lisa [mailto:Christ.Lisa@epa.gov]
Sent: Wednesday, October 04, 2017 11:56 AM
To: Bromberg, Kevin L.; Burneson, Eric; Hafez, Ahmed
Cc: James_H_Kim@ Ex. 6 Personal Privacy (PP) ;Hernandez-Quinones, Samuel
Subject: RE: Perchlorate Charge Question - My latest thoughts - feel free to modify

Kevin,
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You asked: Why do you see less affect (change in fT4 or change in IQ) at the 2.5th percentile than at the 50th percentile? Intuitively you would expect to see a greater affect when the mother has very low fT4, however, the affect is greater at the 50th percentile.

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the distribution around fT4, and the approach to developing distributions for each dose of perchlorate. Additional details on uncertainties can be found in section 6.5.6 of the report.

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Best,

Lisa

From: Bromberg, Kevin L. [mailto:kevin.bromberg@sba.gov]
Sent: Wednesday, October 04, 2017 11:33 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Cc: James_H_Kim Ex. 6 Personal Privacy (PP)
Subject: Perchlorate Charge Question - My latest thoughts - feel free to modify

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    a. Please comment on the assumptions, strengths, and limitations of using the regression analyses to inform the relationship between thyroid hormone levels and neurodevelopmental outcomes.
    b. Please identify additional data or analyses EPA could use to quantify the relationship between thyroid hormone levels and neurodevelopmental effects, including how this information would be expected to improve the analysis.
    c. Please comment on whether there is a magnitude of change in fT4 below which the relationship between fT4 and neurodevelopmental effects should not be used because it is too uncertain.
    d. Please comment on whether other studies that were identified in the literature search (e.g., studies that found effects but lacked statistical significance, studies that did not find an effect, studies that found categorical relationships between fT4 and neurodevelopmental outcomes) could be utilized

to quantitatively characterize the relationship between fT4 and neurodevelopmental outcomes or inform uncertainty associated with the analysis presented.

Kevin Bromberg
Assistant Chief Counsel for Environmental Policy
SBA // Office of Advocacy
409 3rd St. SW, Washington, D.C. 20416
kevin.bromberg@sba.gov 202.481.2963
202.205.6964

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 6/5/2020 11:51:17 AM
To: Parikh, Pooja [Parikh.Pooja@epa.gov]
Subject: FW: Perchlorate
Attachments: 2020.5. NIS allosteric modulation.pdf

Hi Pooja,
WE just became aware of the attached publication related to perchlorate. The study does not change our health effects analysis, however, Jennifer would like to have an EPA response "on the record". What are our options?

Thanks,
Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 29, 2020 12:10 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate

I just got a copy its attached. I will set up a meeting next week with OST to discuss what if any implications there are for our MCLG assessment.

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, May 29, 2020 12:07 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Perchlorate

Hi Eric,

We are trying to get a copy of the paper, as soon as we have it, I will forward a copy of it.

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

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 29, 2020 10:04 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Perchlorate

I was able to locate the abstract at the following site https://www.nature.com/articles/s41594-020-0417-5

From: Burneson, Eric
Sent: Friday, May 29, 2020 9:55 AM
To: Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: RE: Perchlorate

FYI: I have forwarded this story to ORD and OST since we may need their assistance responding to new questions that arise. Let me know if you are able to get a hold of the study referenced below.

Eric

From: Burneson, Eric
Sent: Friday, May 29, 2020 9:06 AM
To: Christ, Lisa (Christ.Lisa@epa.gov) <Christ.Lisa@epa.gov>
Cc: Hernandez-Quinones, Samuel <hernandez.samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: FW: Perchlorate

Vanderbilt researchers find greater thyroid impacts from perchlorate

May 28, 2020

Tweet

Vanderbilt University researchers have published findings indicating the munitions ingredient perchlorate impedes thyroid function more significantly than previously thought, coming shortly after EPA signaled it was unlikely to regulate the substance in drinking water.

In a May 25 article published in the journal *Nature Structural & Molecular Biology*, Vanderbilt researchers found that perchlorate hampers the uptake of iodide, a key component of thyroid hormones, "in a more pronounced and fundamental way than commonly considered," according to an article by Vanderbilt's research news website.

"The end effect of perchlorate exposure on thyroid hormones is that the transport of iodide is impaired," Nancy Carrasco, the paper's lead author and chair of Vanderbilt's Department of Molecular Physiology and Biophysics, says in the article. "Much less iodide will be transported. Now that we understand exactly what perchlorate does, we can clearly see that contamination of drinking water with this chemical is more worrisome than previously thought," she says in the article.

The findings come just as EPA has signaled it will likely pull back on regulating the chemical -- an ingredient in rocket fuel and munitions -- in drinking water. The agency is preparing to issue a final action in June regarding its 2019 proposal on how or whether to regulate perchlorate under the Safe Drinking Water Act (SDWA).

Earlier this month, EPA Administrator Andrew Wheeler noted that due to steps taken by EPA, states and public water systems to identify, monitor and mitigate perchlorate, "the levels have decreased in drinking water."

In a paper EPA released May 14, the agency says it "re-evaluated the available data on the frequency and level of perchlorate occurrence in public water systems," comparing this new data with the lowest potential maximum contaminant level goal that the agency considered in its June 2019 proposed rule.

"The EPA concludes that there is infrequent occurrence of perchlorate at the levels of public health concern. In addition, studies show that perchlorate occurrence in the environment has decreased over time, due to several mitigation actions taken by the EPA and others," it says.

The *New York Times* reported earlier this month that the agency has decided to finalize a rule that calls for no drinking water limits on the chemical. While EPA has not yet sent its final perchlorate drinking water regulatory determination to the White House Office of Management & Budget for review, the *Times* reported that, according to two EPA staff members, the administration will choose to "not impose any limits on perchlorate."

A decision not to regulate the chemical in drinking water would be a second reversal on the issue, after the Obama administration in 2011 reversed the Bush administration's 2008 decision to refrain from regulating the chemical. EPA's signaled action is expected to draw litigation from environmentalists, who say it violates a court order.

In the Vanderbilt study, researchers found that "perchlorate exposure fundamentally alters the mechanism" by which a key protein found in thyroid cells "transports iodide into the thyroid, making it less efficient," the university's article says.

"Even what would be considered low concentrations of perchlorate significantly decrease iodide transport and the resulting production of thyroid hormones," the article says. "Because of thyroid hormones' outsize influence on human cognitive and physical development, the populations most vulnerable to perchlorate-contaminated drinking water are pregnant women, nursing women, developing fetuses, and newborn babies," it says.

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224362

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 9/7/2017 1:54:38 PM
To: Messier, Dawn [Messier.Dawn@epa.gov]
Subject: RE: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release
Attachments: WA459_T3_Vol1 Main Report_170823egb jlm2_lc.docx; WA459_T3_Vol3 AppendixB-G_170823_lc.docx; WA459_T3_Vol2 AppendixA BBDRModel_170823_dfk_pms.2.docx

Hi Dawn,
We are incorporating final edits to the report so we can (hopefully) put it out next week for public comment. Please let me know ASAP if you have any show stopper comments. I'm attaching the version of Vol I with combined edits from Eric, Jennifer and me, Vol II with ORD comments and Vol III with my comments. I can send the unedited versions, but I think it'll be helpful to see what revisions we're working on.

Lisa

From: Messier, Dawn
Sent: Thursday, September 07, 2017 9:38 AM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Cc: Owens, Nicole <Owens.Nicole@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: RE: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release

Thanks for the reminder!

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

From: Flaharty, Stephanie
Sent: Thursday, September 07, 2017 9:34 AM
To: Messier, Dawn <Messier.Dawn@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Cc: Owens, Nicole <Owens.Nicole@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: RE: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release

Dawn,

You concurred on the FR notice in May and the notices have had very only minor edits (see your concurrence email attached).
Also attached are the signed notices.

Lisa - Please send the draft report to Dawn.

Thanks,
Steph

From: Messier, Dawn
Sent: Thursday, September 07, 2017 9:08 AM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Cc: Owens, Nicole <Owens.Nicole@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: RE: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release

Ex. 5 Attorney Client (AC)

I don't recall seeing the FR notices – can someone send me those and the draft report? Thanks.

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

From: Flaharty, Stephanie
Sent: Thursday, September 07, 2017 6:56 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>
Cc: Owens, Nicole <Owens.Nicole@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: RE: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release
Importance: High

OGWDW plans to publish the Perchlorate Peer Review notices now and complete the public 45-day comment periods (for both notices) in time to report to the court that we are making significant progress (in good standing) towards completion of the peer review process. Per the Consent Decree:

> **October 18, 2017**: This is the date by which the decree states that EPA "intends" to complete peer review. If EPA determines that it will not complete the external peer review process by that date, EPA shall file a status report with the court no later than October 30, 2017, describing the progress of the external peer review process, the reason(s) for the delay, and an updated timeline for its completion.

We appreciate assistance in this matter,

Steph Flaharty
Sr. Reg. Mgr./CMS/FOIA Public Liaison
Office of Ground Water and Drinking Water
202.564.5072

From: Evalenko, Sandy
Sent: Wednesday, September 06, 2017 6:11 PM
To: Nurse, Leanne <Nurse.Leanne@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Cc: Owens, Nicole <Owens.Nicole@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>
Subject: Re: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release

Leanne- I'm forwarding your questions to Eric Burneson and Dawn Messier since I don't have the specifics on the consent decree dates.

The FRNs were signed by Mike Shapiro. I'm also not sure about the request for publication on 9/11/17. If we could make public inspection for 9/11 that would be awesome considering these may not go the OFR until Thursday, 8/7. These notices are only 6 pages. Please let us know what you need to move them forward quickly.

Thanks,
Sandy

Sent from my iPhone

On Sep 6, 2017, at 5:45 PM, Nurse, Leanne <Nurse.Leanne@epa.gov> wrote:

> Sandy,
>
> Per discussion with OP management, we need the following information:
>
> - Please provide the specific reference from the consent decree that supports the publication deadline
> - When OW asks for publishing on September 11, 2017, which of the following are you asking for:
> 1) Signature
> 2) FR Public Inspection
> 3) Hard copy publication in the FR
>
> Thank you in advance for providing this information.
>
> Leanne
> 202-566-2207
>
> **From:** Evalenko, Sandy
> **Sent:** Wednesday, September 06, 2017 5:26 PM
> **To:** Nurse, Leanne <Nurse.Leanne@epa.gov>; Owens, Nicole <Owens.Nicole@epa.gov>
> **Cc:** Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Campbell, Ann <Campbell.Ann@epa.gov>; Brown, Sineta <Brown.Sineta@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
> **Subject:** Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release
>
> Leanne/Nicole: I'm walking 2 FRNs on the Perchlorate Peer Review signed by Mike Shapiro today. In order to make the consent decree for Perchlorate, we need to have these publish on 9/11/17. Macara said that the Administrator is supportive of moving this forward quickly to meet the Perchlorate deadlines. Mike Shapiro and Lee Forsgren will be discussing the FRNs with Sarah Greenwalt today at a 5pm meeting to make sure that these move forward quickly. Both FRNs are short (6 pages). If you need additional information please send emails to both Steph and me.

Thanks,
Sandy

From: Flaharty, Stephanie
Sent: Wednesday, September 06, 2017 10:06 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Lousberg, Macara <Lousberg.Macara@epa.gov>; Fields, Wanda <Fields.Wanda@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Tricas, Marisa <tricas.marisa@epa.gov>
Subject: Urgent Attention: REVISED DOCUMENTS Perchlorate Peer Review FRNs for Immediate Release
Importance: High

Sandy / Macara,

Thanks so much for your assistance this morning (on such short notice)! See attached suite of revised documents.

1) To avoid confusion, I've drafted two separate action info. one-pagers and incorporated Macara's comments into both.
2) I've attached the draft Charge document and the Interim Peer Reviewer's biosketches in the package. Lee indicated that they do not need to read the report (300 pp+).
3) I've provided a set of review documents for Lee (in the package).

Let me know if you need anything else...I'm at your beckoned call !

Steph

Message

From: Christ, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=10DBD8E424704E43B5A50F74A4DAC626-LCHRIST]
Sent: 6/2/2020 7:45:58 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Khera, Rajiv [khera.rajiv@epa.gov]
CC: Huff, Lisa [Huff.Lisa@epa.gov]
Subject: FW: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics
Attachments: Response to Peer Review 2 Comments on PFBS Toxicity Assessment.docx; DRAFT Interagency and Agency Tox Assessment for PFBS_May 2020.docx

Hello Gentlemen,
Could one or both of you review the attached PFBS toxicity assessment for a policy level review only? I expect OST to address the science, assessment approach and human health issues. I need you to make sure the assessment does not mischaracterize our program or make unfounded program assertions.

If possible, Alex Lan would like comments by 6/17 so he can consolidate OGWDW response.

Let me know if you have questions or concerns.

Thanks,
Lisa

From: Miller, Gregory <Miller.Gregory@epa.gov>
Sent: Tuesday, June 02, 2020 2:45 PM
To: Lan, Alexis <lan.alexis@epa.gov>
Cc: Strong, Jamie <Strong.Jamie@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics

Hi Alex,
Attached you will find the PFBS Toxicity Assessment that is being shared for internal EPA review through the usual IRIS process. I'm sharing these documents with you as the point of contact for OGWDW. Jennifer McLain has flagged the thyroid (email below) as an area of concern given the perchlorate NPDWS rule withdrawal currently under review at OMB. Please coordinate your response with the perchlorate team in OGWDW (Sam, Rajiv, Lisa) as you draft your comments. Comments are due to ORD by 6/30, but if you could have your comments to me by 6/25, I will combine the OST and OGWDW comments into one document as was requested.

Thanks!

Greg Miller, Senior Environmental Health Scientist
Team Lead, Human Health Risk Assessment Branch
Office of Science and Technology, Health and Ecological Criteria Division
US Environmental Protection Agency, Office of Water
1200 Pennsylvania Ave, NW (MC 4304T)
Washington, DC 20460

phone: (202) 566-2310

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Monday, June 01, 2020 11:31 AM
To: Behl, Betsy <Behl.Betsy@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: PFBS assessment

Betsy – you may already be doing this but I wanted to make sure we are connected to ORD as they respond to their peer review comment: Need for additional clarifying language on the physiology and function of thyroid hormones during pregnancy and further description of the clinical condition "hypothyroxinemia". I'm reviewing the perchlorate response to comment document now and just want to make sure we are being consistent.

Thanks
Jennifer

From: Jones, Samantha <Jones.Samantha@epa.gov>
Sent: Monday, June 1, 2020 5:34 PM
To: Cassidy, Meghan <Cassidy.Meghan@epa.gov>; Olsen, Marian <Olsen.Marian@epa.gov>; Rogers, Rick <rogers.rick@epa.gov>; Gehlhaus, Martin <Gehlhaus.Martin@epa.gov>; Allenbach, Becky <Allenbach.Becky@epa.gov>; Pollard, Solomon <Pollard.Solomon@epa.gov>; Adams, Glenn <Adams.Glenn@epa.gov>; Harris, Kimberly <harris.kimberly@epa.gov>; Mangino, Mario <mangino.mario@epa.gov>; Morton, Michael <Morton.Michael@epa.gov>; Milburn, Anna <Milburn.Anna@epa.gov>; Wooster-Brown, Catherine <Wooster-Brown.Catherine@epa.gov>; Schumacher, Kelly <Schumacher.Kelly@epa.gov>; Bahrman, Sarah <Bahrman.Sarah@epa.gov>; Benson, Bob <Benson.Bob@epa.gov>; Small, Matthew <Small.Matthew@epa.gov>; Stralka, Daniel <Stralka.Daniel@epa.gov>; Allen, Elizabeth <allen.elizabeth@epa.gov>; Anderson-Carnahan, Linda <Anderson-Carnahan.Linda@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>; Barone, Stan <Barone.Stan@epa.gov>; Hamernik, Karen <Hamernik.Karen@epa.gov>; Raffaele, Kathleen <raffaele.kathleen@epa.gov>; Murphy, Deirdre <Murphy.Deirdre@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Hoyer, Marion <hoyer.marion@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>; Dzubow, Rebecca <Dzubow.Rebecca@epa.gov>; Lloyd, Christine <Lloyd.Christine@epa.gov>
Cc: Owens, Beth <Owens.Beth@epa.gov>; Lambert, Jason <Lambert.Jason@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>
Subject: Internal Agency review of the PFBS Toxicity Assessment - link to review materials and logistics

Hello all,

You are receiving this email because you have been identified as your office's point of contact for review of toxicity assessments in general and/or as the PFAS point of contact. If this has reached you by mistake and there is another individual that should be the point person, please let me know as soon as you can.

This email is to initiate the internal agency review of the revised PFBS toxicity assessment. Shortly, you will be granted access to the SharePoint site (see link below) so that you will be able to obtain the PFBS draft toxicity assessment as well as the Response to peer review comments document. Please feel free to circulate the materials within your respective office, we just ask that as the points of contact, that you compile and upload one set of comments from your respective office. We request that you post comments to the SharePoint site by **COB Tuesday, June 30th**.

https://usepa.sharepoint.com/sites/ORD_Work/pfas_toxval_internal_review/SitePages/Home.aspx

We appreciate your feedback. Please let me know if there are any questions.

Thank you!
Samantha

Samantha J. Jones, PhD
Associate Director, Center for Public Health and Environmental Assessment (CPHEA)
National Program Director, Health and Environmental Risk Assessment (HERA) Research Program
Office of Research and Development (ORD)

US Environmental Protection Agency (EPA)
RRB 71210, Washington, DC
(o) 202-564-6794; (m) Ex. 6 Personal Privacy (PP)

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 6/27/2017 4:12:57 PM
To: Albert, Ryan [Albert.Ryan@epa.gov]
Subject: Re: Sodium, Calcium, Potassium Hypochlorite - Preliminary Interim Decision - language for chlorate / perchlorate formation

Sent from my iPhone

On Jun 27, 2017, at 11:47 AM, Albert, Ryan <Albert.Ryan@epa.gov> wrote:

> Of course. Sorry for being spacey and forgetting.
>
> ---
>
> **From:** Christ, Lisa
> **Sent:** Tuesday, June 27, 2017 11:46:09 AM
> **To:** Albert, Ryan
> **Subject:** Re: Sodium, Calcium, Potassium Hypochlorite - Preliminary Interim Decision - language for chlorate / perchlorate formation
>
> Can we talk tomorrow afternoon ? I'm at the lead modeling peer review
>
> Sent from my iPhone
>
> On Jun 27, 2017, at 11:43 AM, Albert, Ryan <Albert.Ryan@epa.gov> wrote:
>
>> Hi Lisa,
>>
>> When are you trying to get comments back to Jessica. Also, do you know why they are highlighting the UCMR chlorate concentrations to NRDC? Any sense as to whether OPP wants to emphasize this point, or they are repeating information first presented to them by NRDC?
>>
>> Thanks,
>>
>> Ryan
>>
>> ---
>>
>> **From:** Christ, Lisa
>> **Sent:** Tuesday, June 27, 2017 10:11:06 AM
>> **To:** Bailey, Jessica
>> **Cc:** Townsend, Clifton; Kyprianou, Rose; Gayoso, Jose; Fehir, Richard; Albert, Ryan; Rodgers-Jenkins, Crystal
>> **Subject:** Re: Sodium, Calcium, Potassium Hypochlorite - Preliminary Interim Decision - language for chlorate / perchlorate formation

Hi Jessica.
Clifton is on detail but I will coordinate with our other branch on reviewing the below.

Sent from my iPhone

On Jun 27, 2017, at 10:04 AM, Bailey, Jessica <bailey.jessica@epa.gov> wrote:

> Good morning Lisa and Clifton,
>
> As you know from our meetings over the past several weeks, OPP-AD is writing the Preliminary Interim Decision for the Hypochlorites Case (Sodium, Calcium, Potassium). Our document will be finalized this Friday, June 30. Below is a section of the document where we discuss possible chlorate and perchlorate formation in stored hypochlorite solutions. The language has been taken from a response letter that OPP-AD had written to NRDC in January 2017 (attached). I was hoping to run this language by you, to be sure it is satisfactory from the Office of Water's standpoint. Of particular interest in the highlighted text.
>
> 1. <!--[if !supportLists]--><!--[endif]-->**Possible Chlorate and Perchlorate Formation in Stored Hypochlorite Solutions**
>
> On July 31, 2014, the National Resource Defense Council (NRDC) wrote a letter to the Agency concerning observations on tolerances for sodium hypochlorite and calcium hypochlorite to minimize degeneration to perchlorate. While the letter fell outside of any currently open registration review comment period for the hypochlorites, EPA did post NRDC's comment letter, along with a formal response letter, to docket EPA-HQ-OPP-2012-0004 at www.regulations.gov.
>
> EPA concurred with the observation in NRDC's letter that research by the American Water Works Association (AWWA) and the Water Research Foundation suggest the potential for perchlorate to form in stored hypochlorite solutions. As noted in the research, AWWA and the Water Research Foundation found hypochlorite concentration, pH, ionic strength, and temperature were major factors impacting perchlorate, and also importantly, chlorate formation in stored hypochlorite solutions at drinking water utilities. Additionally, recent monitoring data included in the EPA Office of Water's Unregulated Contaminant Monitoring Rule (UCMR 3) found increased levels of chlorate in finished drinking water.[1]
>
> There have been reported improvements in industry practices to minimize chlorate and perchlorate formation in stored hypochlorite solutions for drinking water, such as the January 2013 implementation

[1] "EPA Response to NRDC-Observations on Tolerances for Hypochlorite to Minimize Degeneration to Perchlorate, Correspondence" available at https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR&D=EPA-HQ-OPP-2012-0004

of maximum levels of perchlorate and the January 2015 implementation of maximum levels of chlorate per the National Sanitation Foundation (NSF) / American National Standards Institute (ANSI) Standard 60: Drinking Water Treatment Chemicals.[2]

Further, EPA's Office of Water has begun the National Primary Drinking Water Regulation (NPDWR) process for perchlorate. To inform this effort, EPA and Food and Drug Administration scientists are drafting a Biologically Based Dose Response (also known as a Physiologically-Based Pharmacokinetic (PBPK)) model to inform the Agency's Safe Drinking Water Act (SDWA) decision making. In light of this, the Office of Pesticide Programs (OPP) will continue to work with the Office of Water on perchlorate issues during registration review of the hypochlorites.

Thank you so much and I look forward to hearing from you,

Jessica Bailey
Chemical Review Manager
U.S. Environmental Protection Agency
Office: (703) 347-0148

Office of Pesticide Programs
Antimicrobials Division
Regulatory Management Branch II
Location: PYS-8213

<response to NRDC.pdf>

[2] "Chlorine Institute Comment Letter Sodium Hypochlorite Industry Compliance"

Message

From: Christ, Lisa [Christ.Lisa@epa.gov]
Sent: 6/27/2017 4:12:56 PM
To: Townsend, Clifton [Townsend.Clifton@epa.gov]
Subject: Re: Sodium, Calcium, Potassium Hypochlorite - Preliminary Interim Decision - language for chlorate / perchlorate formation

Hi Clifton
I'm at the lead modeling peers review today and tomorrow. Thanks for your input, I'll coordinate with SRRB since they've got the chlorite piece.
Lisa

Sent from my iPhone

On Jun 27, 2017, at 10:09 AM, Townsend, Clifton <Townsend.Clifton@epa.gov> wrote:

> Hi Lisa,
>
> Hope all is well. Are you ok with the language below regarding perchlorate? I have a little reservation about the wording that is highlighted.
>
> Clifton
>
> Further, EPA's Office of Water has begun the National Primary Drinking Water Regulation (NPDWR) process for perchlorate. To inform this effort, EPA and Food and Drug Administration scientists are drafting a Biologically Based Dose Response (also known as a Physiologically-Based Pharmacokinetic (PBPK)) model to inform the Agency's Safe Drinking Water Act (SDWA) decision making. In light of this, the Office of Pesticide Programs (OPP) will continue to work with the Office of Water on perchlorate issues during registration review of the hypochlorites.
>
> **From:** Bailey, Jessica
> **Sent:** Tuesday, June 27, 2017 10:04 AM
> **To:** Christ, Lisa <Christ.Lisa@epa.gov>; Townsend, Clifton <Townsend.Clifton@epa.gov>
> **Cc:** Kyprianou, Rose <Kyprianou.Rose@epa.gov>; Gayoso, Jose <Gayoso.Jose@epa.gov>; Fehir, Richard <Fehir.Richard@epa.gov>
> **Subject:** Sodium, Calcium, Potassium Hypochlorite - Preliminary Interim Decision - language for chlorate / perchlorate formation
>
> Good morning Lisa and Clifton,
>
> As you know from our meetings over the past several weeks, OPP-AD is writing the Preliminary Interim Decision for the Hypochlorites Case (Sodium, Calcium, Potassium). Our document will be finalized this Friday, June 30. Below is a section of the document where we discuss possible chlorate and perchlorate formation in stored hypochlorite solutions. The language has been taken from a response letter that OPP-AD had written to NRDC in January 2017 (attached). I was hoping to run this language by you, to be sure it is satisfactory from the Office of Water's standpoint. Of particular interest in the highlighted text.

1. <!--[if !supportLists]--><!--[endif]-->**Possible Chlorate and Perchlorate Formation in Stored Hypochlorite Solutions**

On July 31, 2014, the National Resource Defense Council (NRDC) wrote a letter to the Agency concerning observations on tolerances for sodium hypochlorite and calcium hypochlorite to minimize degeneration to perchlorate. While the letter fell outside of any currently open registration review comment period for the hypochlorites, EPA did post NRDC's comment letter, along with a formal response letter, to docket EPA-HQ-OPP-2012-0004 at www.regulations.gov.

EPA concurred with the observation in NRDC's letter that research by the American Water Works Association (AWWA) and the Water Research Foundation suggest the potential for perchlorate to form in stored hypochlorite solutions. As noted in the research, AWWA and the Water Research Foundation found hypochlorite concentration, pH, ionic strength, and temperature were major factors impacting perchlorate, and also importantly, chlorate formation in stored hypochlorite solutions at drinking water utilities. Additionally, recent monitoring data included in the EPA Office of Water's Unregulated Contaminant Monitoring Rule (UCMR 3) found increased levels of chlorate in finished drinking water.[1]

There have been reported improvements in industry practices to minimize chlorate and perchlorate formation in stored hypochlorite solutions for drinking water, such as the January 2013 implementation of maximum levels of perchlorate and the January 2015 implementation of maximum levels of chlorate per the National Sanitation Foundation (NSF) / American National Standards Institute (ANSI) Standard 60: Drinking Water Treatment Chemicals.[2]

Further, EPA's Office of Water has begun the National Primary Drinking Water Regulation (NPDWR) process for perchlorate. To inform this effort, EPA and Food and Drug Administration scientists are drafting a Biologically Based Dose Response (also known as a Physiologically-Based Pharmacokinetic (PBPK)) model to inform the Agency's Safe Drinking Water Act (SDWA) decision making. In light of this, the Office of Pesticide Programs (OPP) will continue to work with the Office of Water on perchlorate issues during registration review of the hypochlorites.

Thank you so much and I look forward to hearing from you,

Jessica Bailey
Chemical Review Manager
U.S. Environmental Protection Agency
Office: (703) 347-0148

Office of Pesticide Programs
Antimicrobials Division
Regulatory Management Branch II
Location: PYS-8213

[1] "EPA Response to NRDC-Observations on Tolerances for Hypochlorite to Minimize Degeneration to Perchlorate, Correspondence" available at https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR&D=EPA-HQ-OPP-2012-0004
[2] "Chlorine Institute Comment Letter Sodium Hypochlorite Industry Compliance"

<response to NRDC.pdf>

Appointment

From: Penman, Crystal [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=93662678A6FD4D4695C3DF22CD95935A-PENMAN, CRYSTAL]
Sent: 7/25/2017 1:42:49 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]; linda.s.wennerberg@nasa.gov

Subject: Perchlorate Conference call
Location: Call in Ex. 6 Personal Privacy (PP) passcode Ex. 6 Personal Privacy (PP)

Start: 7/26/2017 8:00:00 PM
End: 7/26/2017 8:30:00 PM
Show Time As: Busy

Message

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

Ex. 5 AC/DP

David Fotouhi

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

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

I just spoke with David Risley regarding his email below and he recommends Ex. 5 AC/DP Ex. 5 AC/DP Ex. 5 AC/DP Let me know if you want me to do something else. Thanks.

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

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

Hey Ariadne,

Ex. 5 AC/DP

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

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

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

As requested.

Ex. 5 Deliberative Process (DP)

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

Ex. 5 Deliberative Process (DP)

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

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

David – do you have more info for her?

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

To: Press <mailto:Press@epa.gov>
Subject: RE: URGENT FOLLOW UP QUESTION FOR EPA: EPA Notes Successes in Reducing Perchlorate in Drinking Water

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

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

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

Amena H. Saiyid
Air & Water Reporter

Bloomberg Industry Group

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

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

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

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

Amena H. Saiyid
Air & Water Reporter

Bloomberg Industry Group

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

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

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

EPA Notes Successes in Reducing Perchlorate in Drinking Water

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

• Remediation activities at 60 Superfund sites to address perchlorate.
• Drinking water regulations for perchlorate in Massachusetts and California.
• Federal and state remediation activities at perchlorate contaminated sites, particularly the ongoing remediation efforts in the state of Nevada to address perchlorate contamination in groundwater adjacent to the lower Colorado River upstream of Lake Mead.

EPA remains committed to continuing to work with states and public water systems and is providing information to water systems on addressing perchlorate in drinking water. For more information on the declining levels of perchlorate in drinking water and information for drinking water utilities:
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-r%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=keSlbQFRQunKej8q8pCjTcS33Ng68zrxFeLSOcNWASQ%3D&reserved=0.

Background

On June 26, 2019, EPA published the notice of proposed rulemaking seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. EPA is developing a final action that reflects comments received on the agency's proposal and will be issued this June. For more information about EPA's proposal, see
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-y%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=LJJSm87Bq9ARHPBuWvkTCf5%2B0W%2F9WDw%2BTRPF2fG83CM%3D&reserved=0.

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

https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-t%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=SV4BMufFPCmYHOH5dbYiEtCz%2BYth3enAvX%2BoOFiUAMg%3D&reserved=0
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-i%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=hHluDMsmtwFMDcDZ3FYcWf0cbGEbFn3GqpKyW%2FSvqig%3D&reserved=0
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-d%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=MY1c64Va4Koxi7Gw5i%2FK5nHXJl3knawF4oUfxweoGN4%3D&reserved=0
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-l-mditrky-alyjhlhdr-h%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=%2FqF0sSnNK%2FGsB9Jc6dWjobO5wJe2PViqUxj5OLcFW08%3D&reserved=0

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue Northwest
Washington, D.C. 20004

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https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fusenvironmentalprotectionagency.cmail20.com%2Ft%2Fd-li-mditrky-alyjhlhdr-o%2F&data=02%7C01%7CForsgren.Lee%40epa.gov%7Cf5cd735f8a2c41ba335108d7f851faed%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637250903300450223&sdata=CD5ZZ0Xyoo9%2FD4EpV%2FVHoco9hnQT07AYoQ9N4K40si8%3D&reserved=0
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Message

From: Parikh, Pooja [Parikh.Pooja@epa.gov]
Sent: 5/14/2020 3:22:24 PM
To: Fotouhi, David [Fotouhi.David@epa.gov]
CC: Wehling, Carrie [Wehling.Carrie@epa.gov]; Neugeboren, Steven [Neugeboren.Steven@epa.gov]; Messier, Dawn [Messier.Dawn@epa.gov]
Subject: Urgent review needed of OW messaging re perchlorate
Attachments: Perchlorate Recommendations for PWS_03.18.2020.formatted.4.docx - psp.docx; Perchlorate Reductions_5.14.20.pdf

Importance: High

David

OW just informed me that they are planning to issue some public messages re perchlorate this afternoon, in response to a press inquiry from the New York Times (see email below). The reporter indicates that she intends to do a story this afternoon, that will say "based on sources, that EPA intends to send to the White House a 'Notice of Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Determination on Perchlorate.'" I have asked

Ex. 5 Deliberative Process (DP)

Could you please let me know ASAP if you have concerns about this messaging, or if you would like to set up time to discuss further. Thanks.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

From: Risley, David
Sent: Thursday, May 14, 2020 9:24 AM
To: Wadlington, Christina <Wadlington.Christina@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: NYT request - 12:00 PM DDL
Importance: High

Christina,
We are heading toward getting some messaging out on perchlorate today. We've been asked to provide the supporting documents and 3-4 key points. Can you reshare the supporting documents and get ready to post them? Don't post yet, but likely early afternoon. I'll mock up some key points and share for your OK.

Best,
David

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

From: Woods, Andrea <Woods.Andrea@epa.gov>
Sent: Thursday, May 14, 2020 8:04 AM
To: Risley, David <Risley.David@epa.gov>; Drinkard, Andrea <Drinkard.Andrea@epa.gov>
Cc: Schiermeyer, Corry <schiermeyer.corry@epa.gov>
Subject: FW: NYT request - 12:00 PM DDL
Importance: High

Hi David,

Please see the below inquiry from Lisa Friedman. Do we have existing language to respond to any of these questions?

From: Lisa Friedman <lisa.friedman@nytimes.com>
Sent: Thursday, May 14, 2020 7:45 AM
To: Schiermeyer, Corry <schiermeyer.corry@epa.gov>; Woods, Andrea <Woods.Andrea@epa.gov>; Press <Press@epa.gov>
Subject: NYT request

Hi guys hope everyone is well.
I will be writing a story this afternoon saying that EPA intends to not regulate perchlorate in drinking water and will revoke the 2011 finding that perchlorate should be regulated. I'd like to get a comment from the agency and my deadline is noon.
Specifically the story will say, based on sources, that EPA intends to send to the White House a "Notice of Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the Final Determination on Perchlorate." As it has been described to me, the notice revokes the 2011 perchlorate finding and justifies that by noting that more more recent analyses show concentrations must be at higher levels than previously thought to be considered unsafe; and that because states like California and Massachusettts are regulating there are now fewer public water systems that contain perchlorate at dangerous levels.
+ Would you be able to confirm that?
+ Can you offer me a comment about why E.P.A. is opting to go this route?
+ What do you say to critics who maintain the agency is making chemical regulatory policies that consistently favor industry over public health?
Secondly, several people have specifically said the policy would set a precedent of allowing for a significant amount of average IQ loss in regulating future chem, since the higher range of 56 ppb for concentration of perchlorate is based on avoiding an average 2 point IQ loss for certain exposed populations.
+ Can you comment on that specifically -- is the EPA no longer considering that level of IQ loss in infants/children an adverse health effect?
+ And finally - EPA has agreed to a consent decree to set a standard by June 2020 -- does this decision mean EPA is not complying with that order?
Thanks very much. I'm at Ex. 6 Personal Privacy (PP) if you want to ring me.
Lisa

--
Lisa Friedman
Reporter, New York Times
(202) 862-0306 office
Ex. 6 Personal Privacy (PP) cell

Message

From: Fotouhi, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FEBAF0D56AAB43F8A9174B18218C1182-FOTOUHI, DA]
Sent: 6/20/2017 12:21:24 AM
To: Michaud, John [Michaud.John@epa.gov]; Lewis, Jen (Lewis.Jen@epa.gov) [Lewis.Jen@epa.gov]
Subject: FW: FFRRO Technical Fact Sheets Update
Attachments: 1-4-Dioxane fact sheet update 5-26-17_508.pdf; FFRRO Fact Sheet -DNT_2-7-17_508.pdf; FFRRO Fact Sheet-Nanomaterials_4-28-17.pdf; FFRRO FactSheet PBDE-PBB update 1-23-17_508.pdf; FFRRO_ECFactSheet_RDX_4-24-17_508.pdf; FFRRO_ECFactSheet_Tungsten_ 4-24-17.pdf; FFRROFactSheet_Contaminants_PFOS PFOA_4-11-17.pdf; FFRROFactSheet_Contaminants_TCP_1-23-17_508.pdf; FFRROFactSheet_Contaminants_TNT_1-23-16_508.pdf; NDMA fact sheet update 1-19-17_508.pdf; Perchlorate_FactSheet 4-24-17.pdf

John, Jen,

Would it be possible for someone in SWERLO to take a look at these draft fact sheets and check the accuracy of the statements made therein, specifically with regard to the regulatory status of each of these contaminants? I would be glad to discuss further. Thanks!

Best,

David

David Fotouhi

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

From: Davis, Patrick
Sent: Friday, June 16, 2017 8:41 AM
To: Fotouhi, David <fotouhi.david@epa.gov>; Brown, Byron <brown.byron@epa.gov>
Subject: FW: FFRRO Technical Fact Sheets Update

David and Byron,

Wanted to get your eyes on these documents before they hit the EPA website. See any red flags?

Thanks,

Patrick Davis
Environmental Protection Agency
Deputy Assistant Administrator, Office of Land and Emergency Management
202-564-3103 office
Ex. 6 Personal Privacy (PP) cell

Information sent to this email address may be subject to FOIA.

From: Cooke, Maryt
Sent: Thursday, June 15, 2017 11:46 AM
To: Breen, Barry <Breen.Barry@epa.gov>; Davis, Patrick <davis.patrick@epa.gov>; Simon, Nigel

<Simon.Nigel@epa.gov>; Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Lowery, Brigid <Lowery.Brigid@epa.gov>; Colip, Matthew <colip.matthew@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>
Subject: FFRRO Technical Fact Sheets Update

Barry/Patrick/Nigel –

FFRRO has updated our Technical Fact Sheets and I wanted to get your approval to move them through the OPA process in preparation of posting them online.

As background, FFRRO has been the lead on these Emerging Contaminant/Technical Fact Sheets since 2005. These fact sheets, available online on the FFRRO website and clu-in.org, provide a summary of the contaminant including physical and chemical properties; environmental and health impacts; existing federal and state guidelines; detection and treatment methods; and additional sources of information. They are generally intended for use by site managers and other field personnel who may address these contaminants at cleanup sites.

FFRRO has developed eleven Technical Fact Sheets based on the needs of EPA staff and in conjunction with the DoD Emerging Contaminants Watch List. They are 1,2,3-trichloropropane (TCP), 1,4-Dioxane, Nanomaterials, N-Nitrosodimethylamine (NDMA), Perchlorate, polybrominated diphenyl ethers (PBDE) and polybrominated biphenyls (PBB), Tungsten, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), dinitrotoluene (DNT), 2,4,6-trinitrotoluene (TNT), and hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). While many of these compounds are more commonly associated with DoD they are not necessarily exclusive to the Services. These fact sheet are also accessed by and available to the public and we have received inquiries on many of them from all over the world.

The last update of the fact sheets occurred about 2 years ago. Since then much of the science and information surrounding these compounds has evolved. One fact sheet of note is the PFOA/PFOS fact sheet. Before the EPA HA was released FFRRO took the PFOA/PFOS factsheet offline so that no confusion would be created by conflicting information in an outdated fact sheet. We have updated the document to be consistent with the HA and most recent information. Several EPA offices have reviewed and offered input on these including OSRTI, ORD, PARMS. The PFOA/S fact sheet has also been reviewed by OW, OEM and ORCR.

We sent these to CPA in anticipation of getting your approval to move forward. Once approve they will continue through the OPA process.

Please let me know if you have any questions or require any additional information. I look forward to your feedback.

Thank you

Mary T. Cooke
USEPA Headquarters
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 5106R (FFRRO)
Washington, DC 20460

Phone: 202-564-0788

Learn about Federal Facility Cleanups in your area:

EEDFacts

Message

From: Vaught, Laura [Vaught.Laura@epa.gov]
Sent: 7/25/2016 6:45:20 PM
To: Grevatt, Peter [Grevatt.Peter@epa.gov]
CC: Burke, Thomas [Burke.Thomas@epa.gov]
Subject: FW: Upcoming OW actions
Attachments: Perchlorate Peer Review Summary 7-22-16.docx

Hi Peter – what's the best way to move forward with the percholorate briefing? Assume you all are taking the lead on setting that up?

From: Beauvais, Joel
Sent: Sunday, July 24, 2016 2:05 PM
To: Adm13McCarthy, Gina <Adm13McCarthy.Gina@epa.gov>
Cc: Fritz, Matthew <Fritz.Matthew@epa.gov>; Vaught, Laura <Vaught.Laura@epa.gov>; Grevatt, Peter <Grevatt.Peter@epa.gov>; Gilinsky, Ellen <Gilinsky.Ellen@epa.gov>
Subject: Upcoming OW actions

Administrator - Sorry for the length of this message, but I leave at 8 am tomorrow for Alaska and wanted to check in with you on a few time sensitive items for this week. I am trying to get on your calendar to talk some time Tuesday, but am not sure if that's possible, so thought I'd send this note. I'm also happy to talk this afternoon or tonight if you happen to have time when you get back from Vienna.

1. EOP Engagement on DW Action Plan: Peter and I are going over to meet with EOP folks on Monday, August 1 to discuss projected substance and timing for the Action Plan. They are asking for us to bring paper then, and seem to strongly prefer that we send something along this week in advance. I have heard that they are interested in October as a time frame for the Action Plan, "to make sure that it gets done". We will need guidance on two issues: (1) what you are comfortable sharing in terms of substance at this juncture; (2) your thoughts on the time frame. From our (OW's) perspective, we prefer November in order to give us time to get all the pieces done; I am also worried that we will rush to get something done in October and then it will get held until mid-November anyway. Having said that, it is not impossible for us to get the Action Plan (and possibly the LCR white paper) done in October. I do not believe we can get the Lead Modeling peer review document done until November, but that could lag (and/or the LCR white paper could lag behind the Action Plan). If we can talk Tuesday, that would be great. (Alaska is 4 hours behind you and I'm available before 12 noon eastern or after 4 pm eastern). If not, Peter is available all this week to meet with you on this.

2. Perchlorate Modeling Peer Review: As you know, we are in the process of negotiating a schedule for the SDWA rulemaking on perchlorate, in response to a mandatory duty suit from NRDC. The schedule we are currently negotiating requires us to initiate, within the next couple weeks, a public HISA peer review of the biologically based dose response model for perchlorate on which we've been working with ORD and FDA, and the proposed approach for applying that model to the derivation of a Maximum Contaminant Level Goal. The peer review document does not include potential MCLGs (let alone MCLs), which would be developed in the context of the forthcoming rulemaking beginning in 2017. However, the document does outline the model and proposed approaches for developing an MCLG and will attract attention. We are briefing up to Tom Burke and Laura Vaught and their staffs this week, and Peter will be working with OPA and OCIR on getting ready to release the peer review document. I am attaching a backgrounder on this, but am writing to ask what you want/need in terms of briefing on this. Do you want us to try to get on your calendar this week or next to discuss, or shall we just work with Tom and Laura and/or others?

3. Nutrients Technical Assistance Memo to States: I am looking to send out to state environmental commissioners, preferably before the August 15 ACWA meeting and ideally the first week of August, a memorandum reaffirming the importance of our work on nutrient pollution and announcing the availability of $600K (possibly a bit more) in technical assistance to assist states on priority actions. This memo is non-regulatory and is a good news story. I've shared with Mark Rupp, Laura Vaught, and the RAs; the Regions have been heavily involved in its development. We've consulted with the states (ACWA and ECOS) and with NACWA on this, all of whom are supportive. Some background is below; I'm happy to share more or to arrange a briefing for you or others if that would be helpful - just let us know what you need.

A number of states have been in contact with me and others in OW, requesting that we do something to reemphasize nutrients as a priority, including by reaffirming the 2011 memo from Nancy Stoner that set a collaborative frame for working with the states on this. I have also recently met with a broad range of ag industry stakeholders, who have similarly expressed their support for continued work under the framework announced in 2011. The key messages of the memo are as follows:

- We've made some important progress in the last 5 years, and a number of states are taking meaningful actions consistent with the 2011 framework
- Nevertheless, nutrient pollution is still the top water quality challenge for the country and requires continued and urgent action
- We continue to support the 2011 framework for collaborative work with the states (which focuses on a range of state work, including work to prioritize watersheds, actions to reduce point and non-point source pollution, and work to support state development of numeric nutrient standards)
- We need to redouble our efforts to address this priority. We'll be reaching out to states to work with them on identifying priority actions going forward, and will be providing $600K+ in technical assistance support for priority actions.

Message

From: Parikh, Pooja [Parikh.Pooja@epa.gov]
Sent: 3/18/2020 6:03:02 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan
Attachments: Draft Perchlorate Compendium HRRCA sections 8-1 to 8-4 rk-lc (002).docx - psp.cw.docx

Sam - please see attached mark-up of the economic assessment comments. Carrie had just a few additional suggestions, which are reflected in the comment bubbles. Please let me know if you have any questions.

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, March 13, 2020 1:07 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan
Importance: High

Hi Pooja,

Will you be able to provide your feedback on the Economic Assessment Responses to comments today?

Also, I am working on another batch of comments that I plan to send to you as soon as Lisa is done with her review. I expect that I will be sending that to you very soon. But we would benefit from seeing your feedback on the first set of comments so that we can try to capture any concerns or guidance you might have on subsequent responses.

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Wednesday, March 11, 2020 2:46 PM

To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Sam –

Apologies but I've been caught up on other matters and haven't had a chance to finish reviewing the Economic Assessment Responses to Comments. I will aim to get comments to you tomorrow.

Ex. 5 Attorney Client (AC)

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, March 11, 2020 9:22 AM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Pooja,

Please let me know if you also have any feedback for me on the Economic Assessment Responses to comments that I sent you last week.

Ex. 5 AC/DP

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Tuesday, March 10, 2020 4:05 PM

To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Ok, I expect I'll have time tomorrow to review.

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, March 10, 2020 3:38 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Pooja,

I am not certain about timing, all I heard was that we needed to have this ready for when the filing takes place. I will get back to you soon about this.

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Tuesday, March 10, 2020 3:03 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Thanks for sending this. Sorry, I haven't had a chance to review yet – but it is on my to-do. What is the timing on this?

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, March 09, 2020 2:15 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Pooja,

Ex. 5 Attorney Client (AC)

This document has been reviewed by Eric and once I get your feedback, I will forward the revised document to the Communications people and to OGWDW.

Thank You
Sam
==========

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

"USEPA Protecting Human Health and the Environment"

Message

From: Wendelowski, Karyn [wendelowski.karyn@epa.gov]
Sent: 12/2/2019 7:59:56 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: Fw: Perchlorate
Attachments: Option Selection for Perchlorate 11-21-19 v1 jlmkw.docx

Hi Sam - resending my comments from last week

From: Wendelowski, Karyn <wendelowski.karyn@epa.gov>
Sent: Wednesday, November 27, 2019 10:50 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Subject: Re: Perchlorate

Hi Eric - attached are a few edits and responses to Jennifer's questions. I've also let DOJ know the decision is now likely to occur mid-December.

Karyn

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, November 26, 2019 4:24 PM
To: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>
Subject: RE: Perchlorate

Karyn:
The briefing has not happened nor is it scheduled. I have asked the team to assume that we will not brief the Administrator until mid December based upon input from OW – IO. Attached is a revised briefing from Jennifer McLain.

If you are in tomorrow it would be good to get your input on a few questions related to this briefing. Thanks

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

From: Wendelowski, Karyn
Sent: Tuesday, November 26, 2019 1:33 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Albert, Ryan <Albert.Ryan@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Behl, Betsy

<Behl.Betsy@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>; Weisman, Richard <Weisman.Richard@epa.gov>
Subject: Perchlorate

Hi All: - DOJ has asked me to check in with you on where we are with respect to schedule and timing. Has a briefing occurred? Any decisions?

Thanks (and Happy Thanksgiving),

Karyn

Karyn Wendelowski
Attorney-Advisor
Water Law Office
Office of General Counsel
(202)564-5493

Message

From: Shao, Nicole [Shao.Nicole@epa.gov]
Sent: 5/9/2019 7:25:31 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: Perchlorate - ORD Input on Narrowed Set of OMB Comments
Attachments: EPA Perchlorate MCL NPRM (OMB 04-30-19)_ord_input_9may19.docx; EPA Perchlorate MCL NPRM (CDC FDA NIH)_ord_input_9may19.docx

Hi Sam,

Thank you for the opportunity to assist in responding to the OMB comments on the draft FRN. Paul and Dustin were able to provide input on all four areas we identified for their review. Their input can be found on the following pages (identified in red below) in the attached documents. Please do not hesitate to contact me if you have any questions. If you need anything else as you are preparing the revised draft for your Management, please don't hesitate to reach out. I'm working tomorrow at my AWL Ex. 6 Personal Privacy (PP)

EPA Perchlorate MCL NPRM (OMB 04-30-19).docx.

Ex. 5 Deliberative Process (DP)

EPA Perchlorate MCL NPRM (CDC FDA NIH).docx
Ex. 5 Deliberative Process (DP)
p. 43 and p. 44.

Nicole

Nicole Shao
US EPA, ORD-Office of Science Policy
1200 Pennsylvania Avenue, NW (8104R)
Washington, DC 20460
(202) 564-6779

From: Shao, Nicole
Sent: Wednesday, May 08, 2019 11:36 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: Perchlorate

Hi Sam,

As discussed, we are not working on anything related to Clewell right now.

Here are the page numbers where I asked NCEA if they could help. So far, Paul responded that the normal vs. positively skewed question related to Table III-1 is something to ask Abt.

NCEA is working to respond to as much as they can of the four areas below by tomorrow. I will be the one sending you our consolidated response. Responses will fall into one of two categories: (1) questions with easy answers, which will be provided, or (2) questions that require additional work to answer that NCEA will flag (answers won't be provided for those by tomorrow). If anything is flagged, we can work with you to determine importance/next steps.

Let's continue to keep our communication pathways open, so ORD is assisting you with what you need most during this tight timeframe.

Thanks,
Nicole

Nicole Shao
US EPA, ORD-Office of Science Policy
1200 Pennsylvania Avenue, NW (8104R)
Washington, DC 20460
(202) 564-6779

From: Shao, Nicole
Sent: Tuesday, May 07, 2019 1:53 PM
To: Lavoie, Emma <Lavoie.Emma@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>
Cc: Burden, Susan <Burden.Susan@epa.gov>
Subject: Perchlorate OMB Comments Review

Emma, Victor,

I spoke with Sam today. Any ORD input needs to be incorporated into a revised draft he has to send to his Management by the end of the week. They will be sharing the revised draft for a quick OMB review early/mid next week and to the Administrator the week of the 20th. The Administrator must sign the proposal by 5/28.

I worked with Sam to focus the places where ORD input would be the most useful. We narrowed the previous list to the following four places. Take a look at what is here. I know it is very tight, but please see if NCEA can provide any input to me by COB Thursday, so I can get it over to Sam for him to use by Friday morning.

EPA Perchlorate MCL NPRM (OMB 04-30-19).docx.

Ex. 5 Deliberative Process (DP)

EPA Perchlorate MCL NPRM (CDC FDA NIH).docx
Pages 43-45. Questions on TSH feedback loop and also fT4.

Thanks,
Nicole

Nicole Shao
US EPA, ORD-Office of Science Policy
1200 Pennsylvania Avenue, NW (8104R)
Washington, DC 20460
(202) 564-6779

Message

From: Parikh, Pooja [Parikh.Pooja@epa.gov]
Sent: 5/21/2020 12:15:31 AM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: RE: Request for Concurrence - Revised Perchlorate FRN
Attachments: Redline Draft Perchlorate FRN 5-19-20.docx - psp.docx

Hi Sam

I've reviewed the changes in the redline version; had only one small tweak to the language on page 6 (and caught a couple of extra commas on page 9). Please see attached. Thanks.

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, May 20, 2020 4:23 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: Request for Concurrence - Revised Perchlorate FRN

Hi Pooja,

We were asked by OW to get OGC's concurrence on the latest version of the FRN before it gets transmitted to OP.

Here I am attaching a redline version that captures the latest changes that we made to the notice since Eric had discussions with OGC. Let me know if you have any questions.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Ryan Klein [Ryan_Klein@abtassoc.com]
Sent: 5/13/2020 10:36:26 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
CC: Lauren_Brown@abtassoc.com; Kaley Beins [Kaley_Beins@abtassoc.com]; Lawrence Reichle [Lawrence_Reichle@abtassoc.com]
Subject: RE: Perchlorate Task
Attachments: Perchlorate Reg Det Withdrawal FR Notice 4-24-20 OCHP comments 050820_Abt Responses.docx

Hi Sam,

I have attached our responses to OCHP's comments to this email. We have included our responses in the comment bubbles as requested. Please let me know if you have any further questions or comments based on our responses.

Thanks so much!

Ryan S. Klein, Ph.D. | Senior Analyst | **Abt Associates**
6130 Executive Boulevard | Rockville, MD 20852
O: 301.634.1814 | www.abtassociates.com
Preferred Pronouns: He/Him/His

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BOLD THINKERS DRIVING REAL-WORLD IMPACT

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, May 12, 2020 2:16 PM
To: Ryan Klein <Ryan_Klein@abtassoc.com>; Lawrence Reichle <Lawrence_Reichle@abtassoc.com>
Cc: Lauren Brown <Lauren_Brown@abtassoc.com>
Subject: FW: Perchlorate Task

Warning from Abt: External email. Be careful opening links and attachments.

FYI

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

"USEPA Protecting Human Health and the Environment"

From: Hernandez-Quinones, Samuel
Sent: Tuesday, May 12, 2020 2:14 PM
To: Lauren Brown <Lauren_Brown@abtassoc.com>
Subject: RE: Perchlorate Task

Hi Lauren,

Here is the document I talked to you about earlier today that I will need your assistance in addressing the comments you will see in the "comment bubbles". Please disregard the comments on pages 18, 19, 23 and 26, as these have to do with occurrence and I will address them separately.

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

"USEPA Protecting Human Health and the Environment"

From: Lauren Brown <Lauren_Brown@abtassoc.com>
Sent: Tuesday, May 12, 2020 12:04 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Perchlorate Task

Hi Sam:
I can call in about 15 minutes will that work?

Lauren

_____
Lauren Brown, MS, DABT | Senior Associate/Scientist | Abt Associates
O: 301.347.5832 | F: 301.828.0859 | www.abtassociates.com
Preferred Pronouns: she/her/hers

Follow Us: **Twitter** | **Facebook** | **LinkedIn**

Schedule Week of 5/4: 7am -1 pm Monday through Friday

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, May 12, 2020 9:54 AM
To: Lauren Brown <Lauren_Brown@abtassoc.com>
Subject: Perchlorate Task

Warning from Abt: External email. Be careful opening links and attachments.

Hi Lauren

I have another task for perchlorate that I will need some assistance from you. It should not take very long but I think it would be good to have a quick 5 minute call so I can talk to you about what needs to be done. Let me know what is a good time to talk.

Thanks
Sam
==========

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

"USEPA Protecting Human Health and the Environment"

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This message may contain privileged and confidential information intended solely for the addressee. Please do not read, disseminate or copy it unless you are the intended recipient. If this message has been received in error, we kindly ask that you notify the sender immediately by return email and delete all copies of the message from your system.

Message

From: Hernandez-Quinones, Samuel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C46D56B82F143DF82F81D322BD109D7-HERNANDEZ-QUINONES, SAMUEL]
Sent: 3/19/2020 4:54:09 PM
To: Parikh, Pooja [Parikh.Pooja@epa.gov]
Subject: Request for Review - Perchlorate Reg Det Withdrawal FRN
Attachments: Draft - Perchlorate Reg Det Withdrawal FR Notice 3-17-20.v1 .docx

Hi Pooja,

Attached you will find the draft FRN announcing the withdrawal of the Reg Det for perchlorate. Lisa has already reviewed this version, let me know what is your availability and timeline for providing your feedback to us.

Also, we will be scheduling a call with you and Carrie in the coming days to have a discussion about OGC's feedback of the HRRCA comments.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C46D56B82F143DF82F81D322BD109D7-HERNANDEZ-QUINONES, SAMUEL]
Sent: 3/19/2020 3:08:25 PM
To: Khera, Rajiv [Khera.Rajiv@epa.gov]
Subject: FW: Request for OGC Review - Court Filing Perchlorate Communications Plan
Attachments: Draft Perchlorate Compendium HRRCA sections 8-1 to 8-4 rk-lc (002).docx - psp.cw.docx

Hi Rajiv,

Ex. 5 Deliberative Process (DP)

Thanks
Sam
==========

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Wednesday, March 18, 2020 2:03 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Sam - please see attached mark-up of the economic assessment comments. Carrie had just a few additional suggestions, which are reflected in the comment bubbles. Please let me know if you have any questions.

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Friday, March 13, 2020 1:07 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>

Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan
Importance: High

Hi Pooja,

Will you be able to provide your feedback on the Economic Assessment Responses to comments today?

Also, I am working on another batch of comments that I plan to send to you as soon as Lisa is done with her review. I expect that I will be sending that to you very soon. But we would benefit from seeing your feedback on the first set of comments so that we can try to capture any concerns or guidance you might have on subsequent responses.

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Wednesday, March 11, 2020 2:46 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Sam –

Apologies but I've been caught up on other matters and haven't had a chance to finish reviewing the Economic Assessment Responses to Comments. I will aim to get comments to you tomorrow.

Ex. 5 Deliberative Process (DP)

Pooja

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

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Wednesday, March 11, 2020 9:22 AM

To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Pooja,

Please let me know if you also have any feedback for me on the Economic Assessment Responses to comments that I sent you last week.

Ex. 5 Attorney Client (AC)

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Tuesday, March 10, 2020 4:05 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Ok, I expect I'll have time tomorrow to review.

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Tuesday, March 10, 2020 3:38 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Pooja,

I am not certain about timing, all I heard was that we needed to have this ready for when the filing takes place. I will get back to you soon about this.

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

"USEPA Protecting Human Health and the Environment"

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Tuesday, March 10, 2020 3:03 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: RE: Request for OGC Review - Court Filing Perchlorate Communications Plan

Thanks for sending this. Sorry, I haven't had a chance to review yet – but it is on my to-do. What is the timing on this?

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, March 09, 2020 2:15 PM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: Request for OGC Review - Court Filing Perchlorate Communications Plan

Hi Pooja,

Ex. 5 Attorney Client (AC)

This document has been reviewed by Eric and once I get your feedback, I will forward the revised document to the Communications people and to OGWDW.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Hernandez-Quinones, Samuel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C46D56B82F143DF82F81D322BD109D7-HERNANDEZ-QUINONES, SAMUEL]
Sent: 9/18/2019 8:18:13 PM
To: Miller, Gregory [Miller.Gregory@epa.gov]
Subject: RE: perchlorate update
Attachments: Perchlorate Comment Summary V4.docx

Hi Greg,

We have requested a 6-month extension of the consent decree deadline and it looks like NRDC has agreed to our request. That would put the deadline to issue a regulatory action by June 2020.

In terms of the proposal we received approximately 1,500 comments. We are currently summarizing and compiling comments. I do not know in what direction we will be going for the final action, but I expect to have a better idea from management by the end of October.

I will send you the compendium for the Health Effects comments by mid-October. But for now, please find the attached high-level summary of the public comments received. Let me know if you have any questions.

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

"USEPA Protecting Human Health and the Environment"

From: Miller, Gregory <Miller.Gregory@epa.gov>
Sent: Wednesday, September 18, 2019 7:57 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: perchlorate update

Hey Sam,
Just checking in. How are things coming along with perchlorate? Has you begun thinking about next steps?

Thanks,

Greg Miller, Senior Environmental Health Scientist
Team Lead, Human Health Risk Assessment Branch
Office of Science and Technology, Health and Ecological Criteria Division
US Environmental Protection Agency, Office of Water
1200 Pennsylvania Ave, NW (MC 4304T)
Washington, DC 20460

phone: (202) 566-2310

Message

From: Hernandez-Quinones, Samuel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C46D56B82F143DF82F81D322BD109D7-HERNANDEZ-QUINONES, SAMUEL]
Sent: 5/21/2020 3:43:40 PM
To: Parikh, Pooja [Parikh.Pooja@epa.gov]
Subject: Request for Concurrence - Revised Perchlorate FRN
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20200521.docx; Redline Draft Perchlorate FRN 5-20-20 .docx

Hi Pooja,

As discussed earlier today, here is the redline version of the revised Perchlorate FRN from FAR. I am also attaching the version that OW will transmit to OP for OMB submittal. Once you are done reviewing this document you can send the concurrence email to me and cc. Lisa Christ.

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

"USEPA Protecting Human Health and the Environment"

Message

From: Evalenko, Sandy [Evalenko.Sandy@epa.gov]
Sent: 5/21/2020 8:45:42 PM
To: Nurse, Leanne [Nurse.Leanne@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]
CC: Manibusan, Mary [Manibusan.Mary@epa.gov]; Lousberg, Macara [Lousberg.Macara@epa.gov]; Ruf, Christine [Ruf.Christine@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]
Subject: Action for OMB review: NPDWR: Perchlorate Final FRN (SAN 5555) to OP for Interagency Review
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20200521.docx; Perchlorate Action Memo 5-19-20.docx; Perchlorate Transmittal Memo AA to OP for OMB Review.pdf; PerchlorateFinal.OGCMemo Style.pdf

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

Thanks,
Sandy

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

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

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

---

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

Hi Charlotte,

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

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

SHARON HAMER

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

Attachments

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

Thank you,
Janita

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

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

Sam,

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

Pooja

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

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

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

Pooja

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

Evalenko, Sandy

From: Flaharty, Stephanie
Sent: Thursday, May 21, 2020 12:47 PM
To: Evalenko, Sandy
Cc: Lousberg, Macara; Ruf, Christine; Brown, Sineta; Fields, Wanda; Tiago, Joseph
Subject: Perchlorate: OGC Concurrence - Revised Perchlorate FRN
Attachments: EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20200521.docx

Importance: High

Hi Sandy,

Attached is OGC-approved FRN and OGC's concurrence (below). I thought I'd check with you to see if you had any edits before I modify the file in CMS. I'll enter OGC's concurrence in CMS now.

Let me know,
Thanks,
Steph

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

Sam,

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

Pooja

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

ED_005043_00222799-00001

Message

From: Muellerleile, Caryn [Muellerleile.Caryn@epa.gov]
Sent: 8/7/2017 11:49:45 AM
To: Johnson, Ann [Johnson.Ann@epa.gov]
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

I intentially bcc'ed the entire list.

From: Johnson, Ann
Sent: Friday, August 04, 2017 4:19 PM
To: Muellerleile, Caryn <Muellerleile.Caryn@epa.gov>
Subject: RE: Interagency briefing on Perchlorate Peer Review hosted by EPA

Caryn,

Was this supposed to go to the list of interagency reviewers? (Sorry I just noticed.)

From: Muellerleile, Caryn
Sent: Friday, August 4, 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: Johnson, Ann [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BF046C29B1604A0E9F712B671C4F3CE5-JOHNSON, ANN]
Sent: 5/22/2020 2:16:43 PM
To: Nickerson, William (Nickerson.William@epa.gov) [Nickerson.William@epa.gov]
Subject: Perchlorate - Some comparisons with FAR version
Attachments: REDLINE with FAR comment bubbles EO12866_SDWA NPDWR 2040-AF28 FRN Perchlorate Rule 20200521.docx

Response to major OP comments…

Basis for Reg Det

FAR Version:

Ex. 5 Deliberative Process (DP)

OMB Version:

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

IQ

Ex. 5 Deliberative Process (DP)

Message

From: Johnson, Ann [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BF046C29B1604A0E9F712B671C4F3CE5-JOHNSON, ANN]
Sent: 5/6/2020 2:36:42 PM
To: Nickerson, William (Nickerson.William@epa.gov) [Nickerson.William@epa.gov]; Corrales, Mark (Corrales.Mark@epa.gov) [Corrales.Mark@epa.gov]
CC: Dockins, Chris [Dockins.Chris@epa.gov]
Subject: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)
Attachments: Draft Perchlorate Reg Det Withdrawal FR Notice 4-24-20 v1 Clean_OP comments.docx

Importance: High

Bill and Mark,

Attached please find staff-level comments on the draft perchlorate notice. I do not have experience with this type of FAR and do not know how comments should be transmitted. Therefore, I will not transmit comments to the workgroup chair unless/until I get your approval to do so. Similarly, I would typically draft a FAR memo with OP's position, but I assume FAR concurrence will be handled differently.

The majority of the attached comments are editorial, but I flagged four substantive comments with a ▒ in the comment bubble (search for ^). These comments are as follows:

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Please let me know if you need anything further. I understand that I do not have an invitation to the FAR meeting.

Ann

From: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Sent: Friday, May 1, 2020 1:48 PM
To: Messier, Dawn <Messier.Dawn@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Foster, Stiven <Foster.Stiven@epa.gov>; Firestone, Michael <Firestone.Michael@epa.gov>; Dzubow, Rebecca <Dzubow.Rebecca@epa.gov>; Shao, Nicole <Shao.Nicole@epa.gov>; Hofmann, Angela <Hofmann.Angela@epa.gov>; Smith, Peterj <Smith.Peterj@epa.gov>; Farrar, Wanda <farrar.wanda@epa.gov>; Raffaele, Kathleen <raffaele.kathleen@epa.gov>
Cc: Prabhu, Aditi <Prabhu.Aditi@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>; Burden, Susan <Burden.Susan@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Miles-McLean, Stuart <Miles-Mclean.Stuart@epa.gov>; Cogliano, Gerain <Cogliano.Gerain@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>
Subject: Urgent: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)
Importance: High

All: This is an Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate Final Action (Tier 1; SAN 5555; RIN: 2040-AF28). The meeting notice was just sent for next **Thursday, May 07, 2020 10:00 AM-10:45 AM;** however, I cannot forward it. Please discuss the meeting with your DAA or AA or their delegee.

OAR and OCSPP: Your AAs participated at an Options discussion meeting about 2 weeks ago. If this FRN is passed down to your office for staff to review, we need someone who works on Perchlorate issues.

Thanks,
Sandy

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Friday, May 01, 2020 1:16 PM
To: Dunn, Alexandra <dunn.alexandra@epa.gov>; Idsal, Anne <idsal.anne@epa.gov>; Briskin, Jeanne <Briskin.Jeanne@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Cook, Steven <cook.steven@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Fischer, David <Fischer.David@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Subject: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)
Importance: High

Good afternoon colleagues,

Thank you for attending the Perchlorate Options Selection meeting in January. As you will see below in my formal message, it is now time for an expedited Final Agency Review for the package. I am sending this to Senior Leadership for each office that has been engaged and I appreciate your help working this quickly through the appropriate levels in your office. Please let me know if you have any questions.

Hope you all are doing well!

Best,
Charlotte
****

This email announces the five day expedited Final Agency Review (FAR) for the **National Primary Drinking Water Regulations: Regulation of Perchlorate.** The FAR meeting will be scheduled on Thursday May 7 at 10:00am EST. Meeting materials are attached. Please submit your comments no later than the FAR meeting for consideration prior to the Office of Water (OW) submitting the document for OMB review.

Pursuant to a consent decree entered by the U.S. District Court for the Southern District of New York, the EPA is required to finalize a national primary drinking water regulation (NPDWR) with a maximum contaminant level goal (MCLG) for perchlorate in drinking water no later than 6/19/2020. The EPA's proposal (84 FR 30524) evaluates the feasibility and affordability of treatment technologies to remove perchlorate from drinking water and examines the costs and benefits of a Maximum Contaminant Level (MCL) and alternative MCLs. The EPA also requested comment on three alterative regulatory options, including withdrawal of the agency's 2011 determination to regulate perchlorate in drinking water.

Final Agency Review is the last point for internal cross-Agency review of this action. It provides a forum for confirming that (1) the workgroup has successfully completed its job and resolved or elevated all issues, (2) the package is complete and ready for OMB review (if necessary), and (3) all Agency and external requirements have been met. Please come to the meeting prepared to represent the position of your Assistant/Associate Administrator at FAR. Your office may take one of the following three positions:

1). If an office has minor, *non-substantive comments,* it may **concur without comment**.

2). If an office has *substantive comments*, it may **concur with comment**. While the lead program should try to resolve the issue(s) raised by the comments, it may choose to go forward to OMB for review, or to the Administrator for signature, without resolving the issues. The lead office is responsible for working with all of the offices that provided substantive comments to determine how to address the comments. If the offices cannot agree on a way to address the

comments, the lead office must include the comments in the action memorandum with an explanation of why it cannot satisfactorily address the comments.

3). If an office feels that *a major issue remains unresolved* (e.g., the action lacks legal authority or conflicts with other EPA rules or policies), it may **non-concur**. Non-concurrence indicates that the AA or RA objects to the action being forwarded to OMB, or to the Administrator for signature.

Please address your FAR memo and any comments to me with ccs to Lisa Christ (Christ.lisa@epa.gov) in OW's Office of Ground Water and Drinking Water, Leanne Nurse in OP (nurse.leanne@epa.gov), and Sandy Evalenko (Evalenko.sandy@epa.gov), OW's Senior Regulatory Manager.

OP's Regulatory Management Division (RMD) will chair the expedited FAR meeting and distribute a memorandum following the meeting that documents all positions provided and any further action agreed upon at the meeting. All comments need to be submitted by the FAR meeting for consideration because of the schedule to quickly submit the action to OMB for review. If a participating Office is not represented at the FAR meeting and has not previously contacted OW in writing prior to the meeting, "concurrence without comment" may be assumed.

Thank you for your assistance in reviewing this action. If you have any questions about the FAR process, please call me 202-564-2453, and if you have questions about the substance of the notice or need more information on the supporting analyses, please contact Lisa Christ at Christ.lisa@epa.gov.

Attachment

Message

From: Johnson, Ann [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BF046C29B1604A0E9F712B671C4F3CE5-JOHNSON, ANN]
Sent: 6/17/2020 6:44:14 PM
To: Corrales, Mark (Corrales.Mark@epa.gov) [Corrales.Mark@epa.gov]
CC: Nurse, Leanne [Nurse.Leanne@epa.gov]
Subject: RE: ACTION/For Signature: Drinking Water: Notice of Final Action on Perchlorate (SAN 5555)
Attachments: Post-OMB changes -10011-21-OW Perchlorate FRN final.Admin.docx

Mark,

OW made some small changes after OMB review. See the ones I flagged with a comment bubble. I assume these are okay?

Also – I realize that my review goes over to a third page. Do you need me to try to cut it back, or does this need to go through quickly?

From: Nurse, Leanne <Nurse.Leanne@epa.gov>
Sent: Wednesday, June 17, 2020 2:23 PM
To: Johnson, Ann <Johnson.Ann@epa.gov>
Subject: Fw: ACTION/For Signature: Drinking Water: Notice of Final Action on Perchlorate (SAN 5555)

fyi - about to load into policy review

From: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Sent: Wednesday, June 17, 2020 2:07 PM
To: Nurse, Leanne <Nurse.Leanne@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>; Lousberg, Macara <Lousberg.Macara@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Subject: ACTION/For Signature: Drinking Water: Notice of Final Action on Perchlorate (SAN 5555)

Leanne: Attached are the files for the Drinking Water: Notice of Final Action on Perchlorate (SAN 5555) for the Administrator's signature. Please let me know if you need anything else. Thank you and Stephanie and others for all your support in moving this forward quickly!!

Sandy

Enclosed are:

The FRN 10011-21-OW Perchlorate FRN final.Admin.docx

Signed Action Memo Perchlorate Action Memo 06.17.2020.pdf
OGC Concurrence Perchlorate FInal OGC Concurrence.pdf

I've already added the typesetting request form to FR Dailies

10011-21-OW Perchlorate Typesetting form.funded.docx Perchlorate Typesetting Request Form 6-4-2020.pdf 10011-21-OW Perchlorate FRN final.Admin.docx

These are the FAR concurrences for the record in ADP Tracker.

Fwd: Perchlorate FRN -- OGC concurs with comment RE: Request for Concurrence - Revised Perchlorate FRN OCHP FAR Memo 05 08 2020.pdf SAN5555_OW_Tier-1_FAR_Final NPDWR (Perc)_OCSPP Response.pdf Perchlorate Typesetting Request Form 6-4-2020.pdf

Message

From: Johnson, Ann [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BF046C29B1604A0E9F712B671C4F3CE5-JOHNSON, ANN]
Sent: 9/25/2019 3:52:52 PM
To: Nurse, Leanne [Nurse.Leanne@epa.gov]
Subject: FW: Perchlorate extension -- NRDC agrees
Attachments: Perchlorate Comment Summary V4.docx

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, September 25, 2019 10:39 AM
To: Miller, Gregory <Miller.Gregory@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate extension -- NRDC agrees

Hi All,
Sorry for the delay in letting you know...we have been granted a six month extension on the consent decree date for the final rule! Attached is a summary of the public comments received on the proposal. Sam is preparing an option selection briefing document. We will start briefing management in mid October. Let us know if you have questions.
thanks,
Lisa

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Wednesday, September 25, 2019 10:24 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: FW: Perchlorate extension -- NRDC agrees

From: Wehling, Carrie
Sent: Wednesday, September 18, 2019 10:37 AM
To: Fotouhi, David <Fotouhi.David@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Neugeboren, Steven <Neugeboren.Steven@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Perchlorate extension -- NRDC agrees

NRDC has agreed to a 6 month extension – DOJ is drafting a stipulation. This is really great news.
Carrie

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

Message

From: Johnson, Ann [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BF046C29B1604A0E9F712B671C4F3CE5-JOHNSON, ANN]
Sent: 9/25/2019 2:43:43 PM
To: Corrales, Mark (Corrales.Mark@epa.gov) [Corrales.Mark@epa.gov]; Curry, Bridgid (Curry.Bridgid@epa.gov) [Curry.Bridgid@epa.gov]
CC: Nickerson, William (Nickerson.William@epa.gov) [Nickerson.William@epa.gov]
Subject: FW: Perchlorate extension -- NRDC agrees
Attachments: Perchlorate Comment Summary V4.docx

I'm guessing this is not news…

From: Christ, Lisa <Christ.Lisa@epa.gov>
Sent: Wednesday, September 25, 2019 10:39 AM
To: Miller, Gregory <Miller.Gregory@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>
Cc: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Perchlorate extension -- NRDC agrees

Hi All,
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To: Fotouhi, David <Fotouhi.David@epa.gov>; Mclain, Jennifer <Mclain.Jennifer@epa.gov>; Neugeboren, Steven <Neugeboren.Steven@epa.gov>; Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Wendelowski, Karyn <wendelowski.karyn@epa.gov>; Rodgers-Jenkins, Crystal <Rodgers-Jenkins.Crystal@epa.gov>
Subject: FW: Perchlorate extension -- NRDC agrees

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Carrie

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

From: Bretz, Emily (USANYS) <Emily.Bretz@usdoj.gov>
Sent: Wednesday, September 18, 2019 10:31 AM
To: Wendelowski, Karyn <wendelowski.karyn@epa.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>; robert.yalen@USDOJ.GOV
Subject: RE: Perchlorate call

Great news. NRDC will stipulate to a 6 month extension on the deadline to finalize. I'll work on drafting a stipulation. It's so nice when reason prevails!

From: Wendelowski, Karyn <wendelowski.karyn@epa.gov>
Sent: Tuesday, September 17, 2019 8:56 AM
To: Bretz, Emily (USANYS) <EBretz@usa.doj.gov>
Cc: Wehling, Carrie <Wehling.Carrie@epa.gov>; Yalen, Robert (USANYS) <RYalen@usa.doj.gov>
Subject: Re: Perchlorate call

Hi Emily - Any news on the extension request?

Thanks,
Karyn

Karyn Wendelowski
Office of General Counsel
(202)564-5493

On Sep 9, 2019, at 9:34 AM, Bretz, Emily (USANYS) <Emily.Bretz@usdoj.gov> wrote:

> I can do anytime tomorrow or late afternoon Wednesday.
>
> Sent from my iPhone
>
> On Sep 9, 2019, at 6:23 AM, Wendelowski, Karyn <wendelowski.karyn@epa.gov> wrote:
>
> **Ex. 5 Attorney Client (AC)**
>
> Thanks,
> Karyn
>
> Karyn Wendelowski
> Office of General Counsel
> (202)564-5493
>
> On Aug 28, 2019, at 9:41 AM, Bretz, Emily (USANYS) <Emily.Bretz@usdoj.gov> wrote:
>
> > Thanks Carrie.
> >
> > ---
> >
> > **From:** Wehling, Carrie <Wehling.Carrie@epa.gov>
> > **Sent:** Wednesday, August 28, 2019 9:37 AM
> > **To:** Yalen, Robert (USANYS) <RYalen@usa.doj.gov>; Bretz, Emily (USANYS) <EBretz@usa.doj.gov>

Cc: Wendelowski, Karyn <wendelowski.karyn@epa.gov>
Subject: NRDC comments on perchlorate fyi

Ex. 5 Attorney Client (AC)

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

Message

From: Burneson, Eric [Burneson.Eric@epa.gov]
Sent: 10/8/2019 8:29:19 PM
To: Tiago, Joseph [Tiago.Joseph@epa.gov]
CC: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: FW: FRN
Attachments: EO 12866 CLEAN LCRR NPRM 10-8-19.docx

Importance: High

Per Jennifer's request attached is the latest FRN version. Note that OMB has not yet cleared this action.

From: Flaharty, Stephanie
Sent: Tuesday, October 08, 2019 11:24 AM
To: Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Cc: Burneson, Eric <Burneson.Eric@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: FRN
Importance: High

Sandy, please send this to the OP FR team for their review! I'm placing a request for publication of the notice on October 24, 2019.

Many thanks,
Steph

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, October 8, 2019 11:19 AM
To: Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: FW: When you have a moment

Stephanie:
Per the suggestion below from Mary and Bill, can you please transmit the attached Draft FRN to EPA's OFR office with a request for an expedited review and request an expedited publication date of 10/24. We should note that the document is not yet cleared or signed but that we expect clearance and signature by Thursday.
Eric

From: Manibusan, Mary
Sent: Tuesday, October 08, 2019 10:51 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>
Subject: RE: When you have a moment

Hi Eric,

The perchlorate proposal was received by OP on May 24th and the FRN was submitted to OFR on June 10th with comments and responses delaying the publication until June 26th. With the size of the FRN being 300 pages in length, I would advise sending the document to OFR ASAP, with a request for an expedited review and publication date. As Bill indicated, it is at the discretion of OFR to grant/deny the request, but it will at least flag it as a priority. And as with the proposal, I would anticipate comments from OFR prior to publication. Please let me know if you have additional questions.

Mary

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Tuesday, October 8, 2019 10:07 AM
To: Nickerson, William <Nickerson.William@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: RE: When you have a moment

Thanks Bill
On 3 we are remembering a one month lag between signature (May 23)and FRN publication (June 26) of the perchlorate proposal which we understood was due to delays in transmitting to OFR. Given the Administrator's aggressive schedule for a final rule (he had us put January in the Reg Agenda) we need to do everything we can to expedite. I realize this may not be sufficient for the OFR but I guess I am checking on what we can do to get this in their queue for publication ASAP. Note that the FRN is over 300 pages in length.
Eric

From: Nickerson, William
Sent: Tuesday, October 08, 2019 9:17 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>
Subject: RE: When you have a moment

I assume 1 and 2 are inevitable.

On 3, we can quickly transmit to OFR and expeditiously deal with any edits that come back. Are you looking for something more than that? It is possible to send a package to OFR with a request to expedite, but OFR is pretty strict about offering a good reason for that (because it's important isn't enough).

Copying Mary in case she has been in contact with OW WPS already on this.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, October 07, 2019 6:33 PM
To: Nickerson, William <Nickerson.William@epa.gov>
Subject: When you have a moment

Bill
I need to check in with you about

1. expedited loading of the final FRN /EA in to ROCIS for the LCRR and
2. expedited processing of the FRN for Autopen signature in time for Thursday's rollout by the Administrator
3. expedited FRN processing following Administrator's signature to assure we don't have a significant lag before publication.

Perhaps the OW WPS staff have already worked this through but I wanted to be certain its on OP's radar.
Can we talk in the morning?
Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

Message

From: Wehling, Carrie [Wehling.Carrie@epa.gov]
Sent: 5/4/2020 8:38:37 PM
To: Parikh, Pooja [Parikh.Pooja@epa.gov]
Subject: RE: My mark-up of perchlorate FRN
Attachments: Draft Perchlorate Reg Det Withdrawal FR Notice 4-24-20 v1 - FAR - psp.cw.docx

With my comments, and responding to your bubble comments. Feel free to erase any of my comments as you move this forward.
When you are ready, do you want to send this version to Dawn, Steve and David? I believe FAR is on Thursday morning and I assume we will recommend to David to concur, with the assumption that our markup comments will be addressed? I will confirm with him tomorrow that he is attending to represent OGC, or if he wants one of us to do that (it's the same time as Hot Issues).
Thanks.
Carrie

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Monday, May 04, 2020 10:52 AM
To: Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: My mark-up of perchlorate FRN

Please see attached; thanks.

Pooja

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

From: Wehling, Carrie <Wehling.Carrie@epa.gov>
Sent: Monday, May 04, 2020 8:15 AM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)

Thanks, Pooja. I will look at it this afternoon.
Carrie

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Monday, May 04, 2020 8:14 AM
To: Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: RE: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)

FYI – I am reviewing this right now; will get my mark-up to you later this morning, so you can review my comments and add in your own.

From: Wehling, Carrie <Wehling.Carrie@epa.gov>
Sent: Friday, May 01, 2020 1:24 PM
To: Fotouhi, David <Fotouhi.David@epa.gov>
Cc: Neugeboren, Steven <Neugeboren.Steven@epa.gov>; Parikh, Pooja <Parikh.Pooja@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: Re: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)

Yes we did. We've commented on two rounds before this one. We will review this as well and let you know if we see any issue of significant concern.

Sent from my iPhone

On May 1, 2020, at 1:18 PM, Fotouhi, David <Fotouhi.David@epa.gov> wrote:

FYI. I know that you all have been working with the OW team on this and assume you had the opportunity to provide comments on a previous draft, but please let me know if that's not the case. Thank you!

David Fotouhi

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

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Friday, May 1, 2020 1:16 PM
To: Dunn, Alexandra <dunn.alexandra@epa.gov>; Idsal, Anne <idsal.anne@epa.gov>; Briskin, Jeanne <Briskin.Jeanne@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Cook, Steven <cook.steven@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Orme-Zavaleta, Jennifer <Orme-

Zavaleta.Jennifer@epa.gov>; Fischer, David <Fischer.David@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Subject: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)
Importance: High

Good afternoon colleagues,

Thank you for attending the Perchlorate Options Selection meeting in January. As you will see below in my formal message, it is now time for an expedited Final Agency Review for the package. I am sending this to Senior Leadership for each office that has been engaged and I appreciate your help working this quickly through the appropriate levels in your office. Please let me know if you have any questions.

Hope you all are doing well!

Best,
Charlotte
****

This email announces the five day expedited Final Agency Review (FAR) for the **National Primary Drinking Water Regulations: Regulation of Perchlorate.** The FAR meeting will be scheduled on Thursday May 7 at 10:00am EST. Meeting materials are attached. Please submit your comments no later than the FAR meeting for consideration prior to the Office of Water (OW) submitting the document for OMB review.

Pursuant to a consent decree entered by the U.S. District Court for the Southern District of New York, the EPA is required to finalize a national primary drinking water regulation (NPDWR) with a maximum contaminant level goal (MCLG) for perchlorate in drinking water no later than 6/19/2020. The EPA's proposal (84 FR 30524) evaluates the feasibility and affordability of treatment technologies to remove perchlorate from drinking water and examines the costs and benefits of a Maximum Contaminant Level (MCL) and alternative MCLs. The EPA also requested comment on three alterative regulatory options, including withdrawal of the agency's 2011 determination to regulate perchlorate in drinking water.

Final Agency Review is the last point for internal cross-Agency review of this action. It provides a forum for confirming that (1) the workgroup has successfully completed its job and resolved or elevated all issues, (2) the package is complete and ready for OMB review (if necessary), and (3) all Agency and external requirements have been met. Please come to the meeting prepared to represent the position of your Assistant/Associate Administrator at FAR. Your office may take one of the following three positions:

1). If an office has minor, *non-substantive comments,* it may **concur without comment**.

2). If an office has *substantive comments*, it may **concur with comment**. While the lead program should try to resolve the issue(s) raised by the comments, it may choose to go forward to OMB for review, or to the Administrator for signature, without resolving the issues. The lead office is responsible for working with all of the offices that provided substantive comments to determine how to address the comments. If the offices cannot agree on a way to address the comments, the lead office must include the comments in the action memorandum with an explanation of why it cannot satisfactorily address the comments.

3). If an office feels that *a major issue remains unresolved* (e.g., the action lacks legal authority or conflicts with other EPA rules or policies), it may **non-concur**. Non-concurrence indicates that the AA or RA objects to the action being forwarded to OMB, or to the Administrator for signature.

Please address your FAR memo and any comments to me with ccs to Lisa Christ (Christ.lisa@epa.gov) in OW's Office of Ground Water and Drinking Water, Leanne Nurse in OP (nurse.leanne@epa.gov), and Sandy Evalenko (Evalenko.sandy@epa.gov), OW's Senior Regulatory Manager.

OP's Regulatory Management Division (RMD) will chair the expedited FAR meeting and distribute a memorandum following the meeting that documents all positions provided and any further action agreed upon at the meeting. All comments need to be submitted by the FAR meeting for consideration because of the schedule to quickly submit the action to OMB for review. If a participating Office is not represented at the FAR meeting and has not previously contacted OW in writing prior to the meeting, "concurrence without comment" may be assumed.

Thank you for your assistance in reviewing this action. If you have any questions about the FAR process, please call me 202-564-2453, and if you have questions about the substance of the notice or need more information on the supporting analyses, please contact Lisa Christ at Christ.lisa@epa.gov.

Attachment

<Draft Perchlorate Reg Det Withdrawal FR Notice 4-24-20 v1 Clean.docx>

Message

From: Wehling, Carrie [Wehling.Carrie@epa.gov]
Sent: 3/30/2020 12:59:24 AM
To: Parikh, Pooja [Parikh.Pooja@epa.gov]
Subject: RE: Perchlorate FRN for your review
Attachments: Perchlorate Reg Det Withdrawal FR Notice 3-20-20.v2.docx - psp.cw.docx

Thanks, Pooja. Here are my comments/thoughts. Happy to chat.
Carrie

Caroline (Carrie) Wehling
Assistant General Counsel
Water Law Office
U.S. Environmental Protection Agency
Washington DC 20004
202-564-5492
wehling.carrie@epa.gov

From: Parikh, Pooja <Parikh.Pooja@epa.gov>
Sent: Tuesday, March 24, 2020 4:08 PM
To: Wehling, Carrie <Wehling.Carrie@epa.gov>
Subject: Perchlorate FRN for your review

Hi Carrie

I am attaching my mark-up of the FRN for our withdrawal of the reg det for perchlorate. I have flagged some questions for you in the comment bubbles. In terms of timing, Sam Hernandez says they are looking to submit the package to OW's front office by 4-6-20.

Thanks.

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

Message

From: Parikh, Pooja [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=5572FACE2E61429CB6F14C3864554CCA-PARIKH, POOJA]
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To: Wehling, Carrie [Wehling.Carrie@epa.gov]
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Attachments: Draft Perchlorate Reg Det Withdrawal FR Notice 4-24-20 v1 - FAR - psp.docx

Please see attached; thanks.

Pooja

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

From: Wehling, Carrie <Wehling.Carrie@epa.gov>
Sent: Monday, May 04, 2020 8:15 AM
To: Parikh, Pooja <Parikh.Pooja@epa.gov>
Subject: RE: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)

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202-564-5492
wehling.carrie@epa.gov

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Sent: Friday, May 01, 2020 1:24 PM
To: Fotouhi, David <Fotouhi.David@epa.gov>

Cc: Neugeboren, Steven <Neugeboren.Steven@epa.gov>; Parikh, Pooja <Parikh.Pooja@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>
Subject: Re: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)

Yes we did. We've commented on two rounds before this one. We will review this as well and let you know if we see any issue of significant concern.

Sent from my iPhone

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David Fotouhi

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

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To: Dunn, Alexandra <dunn.alexandra@epa.gov>; Idsal, Anne <idsal.anne@epa.gov>; Briskin, Jeanne <Briskin.Jeanne@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Cook, Steven <cook.steven@epa.gov>; Bolen, Brittany <bolen.brittany@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Fischer, David <Fischer.David@epa.gov>
Cc: Manibusan, Mary <Manibusan.Mary@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Tovar, Katlyn <tovar.katlyn@epa.gov>; Nurse, Leanne <Nurse.Leanne@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>; McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Subject: Expedited Final Agency Review: National Primary Drinking Water Regulations: Regulation of Perchlorate (Tier 1; SAN 5555; RIN: 2040-AF28)
Importance: High

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Final Agency Review is the last point for internal cross-Agency review of this action. It provides a forum for confirming that (1) the workgroup has successfully completed its job and resolved or elevated all issues, (2) the package is complete and ready for OMB review (if necessary), and (3) all Agency and external requirements have been met. Please come to the meeting prepared to represent the position of your Assistant/Associate Administrator at FAR. Your office may take one of the following three positions:

1). If an office has minor, *non-substantive comments,* it may **concur without comment**.

2). If an office has *substantive comments*, it may **concur with comment**. While the lead program should try to resolve the issue(s) raised by the comments, it may choose to go forward to OMB for review, or to the Administrator for signature, without resolving the issues. The lead office is responsible for working with all of the offices that provided substantive comments to determine how to address the comments. If the offices cannot agree on a way to address the comments, the lead office must include the comments in the action memorandum with an explanation of why it cannot satisfactorily address the comments.

3). If an office feels that *a major issue remains unresolved* (e.g., the action lacks legal authority or conflicts with other EPA rules or policies), it may **non-concur**. Non-concurrence indicates that the AA or RA objects to the action being forwarded to OMB, or to the Administrator for signature.

Please address your FAR memo and any comments to me with ccs to Lisa Christ (Christ.lisa@epa.gov) in OW's Office of Ground Water and Drinking Water, Leanne Nurse in OP (nurse.leanne@epa.gov), and Sandy Evalenko (Evalenko.sandy@epa.gov), OW's Senior Regulatory Manager.

OP's Regulatory Management Division (RMD) will chair the expedited FAR meeting and distribute a memorandum following the meeting that documents all positions provided and any further action agreed upon at the meeting. All comments need to be submitted by the FAR meeting for consideration because of the schedule to quickly submit the action to OMB for review. If a participating Office is not represented at the FAR meeting and has not previously contacted OW in writing prior to the meeting, "concurrence without comment" may be assumed.

Thank you for your assistance in reviewing this action. If you have any questions about the FAR process, please call me 202-564-2453, and if you have questions about the substance of the notice or need more information on the supporting analyses, please contact Lisa Christ at Christ.lisa@epa.gov.

Attachment

<Draft Perchlorate Reg Det Withdrawal FR Notice 4-24-20 v1 Clean.docx>

Message

From: Parikh, Pooja [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=5572FACE2E61429CB6F14C3864554CCA-PARIKH, POOJA]
Sent: 3/24/2020 8:07:54 PM
To: Wehling, Carrie [Wehling.Carrie@epa.gov]
Subject: Perchlorate FRN for your review
Attachments: Perchlorate Reg Det Withdrawal FR Notice 3-20-20.v2.docx - psp.docx

Hi Carrie

I am attaching my mark-up of the FRN for our withdrawal of the reg det for perchlorate. I have flagged some questions for you in the comment bubbles. In terms of timing, Sam Hernandez says they are looking to submit the package to OW's front office by 4-6-20.

Thanks.

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

Appointment

From: Pachon, Carlos [Pachon.Carlos@epa.gov]
Sent: 7/7/2017 1:07:26 PM
To: Pachon, Carlos [Pachon.Carlos@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]; Simes, Benjamin [Simes.Benjamin@epa.gov]
CC: Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Laija, Emerald [Laija.Emerald@epa.gov]; Kelley, Meghan [kelley.meghan@epa.gov]; Burchette, John [Burchette.John@epa.gov]; Cynthia Manson (cjm@indecon.com) [cjm@indecon.com]

Subject: Remediation Market Study - Federal Agency analysis preview 866 2993188 7036039903 Texas Room at FFRRO
Attachments: Federal Facilities Chapter_6.13.2017.docx

Start: 7/13/2017 8:00:00 PM
End: 7/13/2017 8:45:00 PM
Show Time As: Busy

Seeking time with you to share our preliminary analysis of future remediation work by Federal Agencies

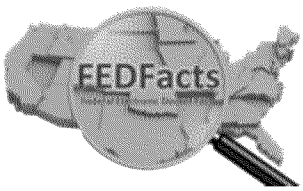
To: Cooke, Maryt[Cooke.Maryt@epa.gov]; Davison, Jenny[davison.jenny@epa.gov]
Cc: Bertrand, Charlotte[Bertrand.Charlotte@epa.gov]; Gervais, Gregory[Gervais.Gregory@epa.gov]
From: Burchette, John[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=510E63474EF14C248511311CC9117DCB-JBURCHET]
Sent: Mon 10/2/2017 5:45:05 PM (UTC)
Subject: FF NPL Perchlorate Decisions
Untitled Analysis.xlsx

All,
I found Perchlorate listed as a COC at 15 FF NPL OU's. I wouldn't consider the SEMS data to be comprehensive, but should be a good start. These, for the most part, should be decision documents which you should be able to search from the RODs database: https://www.epa.gov/superfund/search-superfund-decision-documents

Let me know if you need any additional info

John Burchette
Office of Land and Emergency Management
Federal Facilities Restoration and Reuse Office – 5106R
Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460
Phone: 202-564-3338
Cell: 571-329-4523

Learn about Federal Facility Cleanups in your area:



Region	Site Name	OU	NPL Status	Federal Facility Flag
01	OTIS AIR NATIONAL GUARD BASE/CAMP EDWARDS	16	Currently on the Final NPL	Y
		24	Currently on the Final NPL	Y
03	INDIAN HEAD NAVAL SURFACE WARFARE CENTER	10	Currently on the Final NPL	Y
04	USARMY/NASA REDSTONE ARSENAL	10	Currently on the Final NPL	Y
		19	Currently on the Final NPL	Y
06	LONGHORN ARMY AMMUNITION PLANT	04	Currently on the Final NPL	Y
		18	Currently on the Final NPL	Y
	PANTEX PLANT (USDOE)	01	Currently on the Final NPL	Y
09	EDWARDS AIR FORCE BASE	04	Currently on the Final NPL	Y
		11	Currently on the Final NPL	Y
	EL TORO MARINE CORPS AIR STATION	08	Currently on the Final NPL	Y
	JET PROPULSION LABORATORY (NASA)	01	Currently on the Final NPL	Y
		03	Currently on the Final NPL	Y
	LAWRENCE LIVERMORE NATL LAB (SITE 300) (USDOE)	08	Currently on the Final NPL	Y
	MCCLELLAN AIR FORCE BASE (GROUND WATER CONTAMINATION)	01	Currently on the Final NPL	Y

Media Name	Contaminant
Groundwater	PERCHLORATE
Groundwater	PERCHLORATE
Soil	PERCHLORATE
Groundwater	PERCHLORATE
Subsurface Soil	PERCHLORATE
Surface Soil	PERCHLORATE
Groundwater	PERCHLORATE
Groundwater	PERCHLORATE
Soil	PERCHLORATE
Lhaap-50 Groundwater	PERCHLORATE
Lhaap-50 Soil	PERCHLORATE
Zone 11 Groundwater	PERCHLORATE
Ou 4 & 9 Groundwater	PERCHLORATE
Site 115 Debris	PERCHLORATE
Site 36 Gw	PERCHLORATE
Site 36 Soil	PERCHLORATE
Irp Site 1 Source Gw	PERCHLORATE
Groundwater	PERCHLORATE
Off-Facility Gw	PERCHLORATE
Groundwater	PERCHLORATE
Ou3 Groundwater	PERCHLORATE
Ou4 Groundwater	PERCHLORATE
Ou5 Bldg 850 Gw	PERCHLORATE
Ou5 Pit 7 Gw	PERCHLORATE
Ou6 Groundwater	PERCHLORATE
Ou7 Groundwater	PERCHLORATE
Ou8 Bld801/Pit8lf Gw	PERCHLORATE
Gw Ou01	PERCHLORATE

Title
FINAL RECORD OF DECISION FOR LANDFILL 1 SOURCE AREA AND GROUNDWATER, WITH TRANSMITTAL DATED 10/5/07
FINAL CHEMICAL SPILL-19 GROUNDWATER PLUME INTERIM RECORD OF DECISION (ROD)
FINAL CHEMICAL SPILL-19 RECORD OF DECISION
RECORD OF DECISION (ROD) - SITE 39
FINAL RECORD OF DECISION FOR SURFACE MEDIA AT RSA-011, FORMER SEWAGE TREATMENT PLANT NO. 1 OPERABLE UNIT 10, US ARMY/NASA REDSTONE ARSENAL.
FINAL RECORD OF DECISION RSA-99, ABANDONED PLATING SHOP TANKS AND SUMP BUILDING 7614 OPERABLE UNIT 10, US ARMY/NASA REDSTONE ARSENAL.
FINAL RECORD OF DECISION FOR SURFACE MEDIA AT RSA-011, FORMER SEWAGE TREATMENT PLANT NO. 1 OPERABLE UNIT 10, US ARMY/NASA REDSTONE ARSENAL.
FINAL RECORD OF DECISION FOR SURFACE MEDIA AT RSA-011, FORMER SEWAGE TREATMENT PLANT NO. 1 OPERABLE UNIT 10, US ARMY/NASA REDSTONE ARSENAL.
FINAL INTERIM RECORD OF DECISION INTERIM REMEDIAL ACTION FOR INSTALLATION-WIDE GROUNDWATER FOR THE US ARMY/NASA REDSTONE ARSENAL SITE
RECORD OF DECISION SEPTEMBER 2008 FOR GROUNDWATER, SOIL AND ASSOCIATED MEDIA FOR PANTEX PLANT
Final record of decision (ROD), S Air Force Research Laboratory, OUs 4 & 9, Edwards Air Force Base, w/apps A-E (04 ROD Complete 003, 9/24/07)
Final record of decision (ROD), Air Force Research Laboratory soil & debris sites, OUs 4 & 9, Edwards AFB, 5/08, w/apps A-D (11 RI/FS Actual Complete LW 013) (11 ROD
Final record of decision (ROD), Air Force Research Laboratory soil & debris sites, OUs 4 & 9, Edwards AFB, 5/08, w/apps A-D (11 RI/FS Actual Complete LW 013) (11 ROD
Final record of decision (ROD), Air Force Research Laboratory soil & debris sites, OUs 4 & 9, Edwards AFB, 5/08, w/apps A-D (11 RI/FS Actual Complete LW 013) (11 ROD
Final interim record of decision (ROD), OU 1, w/apps A-B & attchs (supporting documentation), (01 ROD 001, 2/8/07)
Final interim record of decision (ROD) for operable unit (OU) 3 off-facility groundwater, w/app A (03 ROD 003)
Final non-VOC amendment to basewide VOC groundwater record of decision (ROD), w/apps A-B & TLs (01 ROD Amendment FF 1, 8/31/09)

Message

From: Burchette, John [Burchette.John@epa.gov]
Sent: 7/27/2017 10:27:37 PM
To: Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Treimel, Ellen [Treimel.Ellen@epa.gov]
CC: Burchette, John [Burchette.John@epa.gov]
Subject: EI-HENC Detailed 0727171820jb.xlsx
Attachments: EI-HENC Detailed 0727171820jb.xlsx

Charlotte,
Here you go (I was about halfway into it so I just finished it). Let me know if you need anything else.

Region	State	Site Name	NPL Status	Federal Facility Flag	Federal Agency	Brac Name	EI Human Exp Survey Result	HE Justification Change Description	HE Last Review Date	HE Estimated Exposure Control Date	HE Pathway
02	PR	ATLANTIC FLEET WEAPONS TRAINING AREA	Currently on the Final NPL	Y			Current Human Exposure Not Controlled	see exposure pathway description	9/30/2016	9/30/2025 12:00:00 AM	There is insufficient information to determine the site-wide human exposure status at the Atlantic Fleet Weapons Training Area - Vieques Superfund Site. The Atlantic Fleet Weapons Training Area - Vieques, includes certain areas of the island of Vieques and nearby waters that have become contaminated primarily by United States Department of Defense (DoD) activities. From the 1940s until 2003, the US Navy administered lands on both the western and eastern ends of Vieques Island. The lands were used for military training and operations (ship-to-shore gun fire, air-to-ground bombing by naval aircraft, Marine amphibious landing, or combinations), and to store munitions for Atlantic Fleet training. Extensive amounts of unexploded ordnance and remnants of exploded ordnance have been identified in the range areas of Vieques, and in the surrounding waters. The Navy is currently

											conducting a removal of all surface munitions and explosives of concern in the impact area in east Vieques. This action needs to be completed before a comprehensive study to evaluate the nature and extent of the contamination can be performed. Currently, hazardous substances that may be present at the site have not been fully characterized, but may include mercury, lead, copper, magnesium, lithium, perchlorate, TNT, napalm, depleted uranium, PCBs, solvents, and pesticides. As soon as the time critical removal action of unexploded ordnance is complete, the Navy will conduct an RI/FS to define the nature and extent of the contamination. EPA ensures community participation throughout the remedial process by meeting with residents and affected stakeholders, issuing public notices and updating fact sheets. A site profile has been established on the EPA website to keep the community informed of recent progress at the site. Additionally, an EPA Community Involvement Coordinator is assigned to the site and can address specific community concerns as they arise

04	FL	TYNDALL AIR FORCE BASE	Currently on the Final NPL	Y	Department of Defense		Current Human Exposure Not Controlled		11/23/2016	9/30/2017 12:00:00 AM	The Tyndall Air Foce Base is considered Human Exposure Not Under Control. DDT is reported in fish and sediments throughout Shoal Point Bayou. The levels of contaminants to which humans are exposed do not fall within levels designated as safe by EPA. The 2002 RI for Shoal Point Bayou concluded that consumption of fish and shellfish from the Bayou should not be permitted in order to be protective of human health at the 1 x 10-4 risk level. Similarly, dermal contact with DDT in the Bayou was found to present an unacceptable risk to waders. It is reasonable to expect that people come into contact with contaminated media at this waste unit. Tyndall AFB representatives have informed EPA that private boats enter Shoal Point Bayou for recreational fishing and wading. There are no physical barriers to prevent public access by water or by land to the DDT contaminated media. EPA issued a RCRA 7003 imminent and substantial endangerment Order to the Air Force on November 21, 2007, to address base-wide contaminant conditions at Tyndall Air Force Base. The Order sets deadlines for Air Force development of enforceable schedules for cleanup activities. These activties will include early actions by the Air Force, such as improved warning signage and community outreach regarding fish consumption and wading hazards, to

											mitigate unacceptable exposures to contaminants at OT29 pending final cleanup of the Bayou.
08	UT	HILL AIR FORCE BASE	Currently on the Final NPL	Y	US Air Force		Current Human Exposure Not Controlled	Basewide Indoor Air Sampling is ongoing. Vapor removal systems have been installed and based on the results of future sampling more vapor removal systems may be installed.	6/1/2017	9/30/2018 12:00:00 AM	The Hill Air Force Base Superfund site is considered "Current Human Exposure Not Under Control" because potential exposure to vapors from contaminated groundwater entering residences is still under investigation. The Air Force has developed a program to investigate as many as 2600 residences and install vapor extraction systems where needed to protect human health for the short term. Remedial actions are in place to address the contaminants in ground water, which will address the source of the vapors in the long term. There is an ongoing community outreach program at the Base.
09	CA	FORT ORD	Currently on the Final NPL	Y	Department of Defense	BRAC 2	Current Human Exposure Not Controlled	Despite fencing, signage, police patrols, community mailings, briefings in schools, and removal actions to protect population from exposure to unexploded ordnance across over 8000 acres, it is difficult to keep trespassers out of an area	5/24/2017	9/30/2020 12:00:00 AM	The Fort Ord Superfund site is considered Human Exposure Not Under Control because trespassers can come into contact with munitions and explosives of concern (MEC), specifically in the 8000 acre impact range. As of April 2009, U.S. Army has installed fences throughout impacted areas, posted signs advising against entering the area, sent fact sheets about the site, and conducted briefings in local schools encouraging people

								surrounded by 11 miles of fencing because some areas remote. Exposure could result in great bodily harm or death.			not to enter the site, but trespassing continues, putting people in danger from contact with explosives. In 2008, the Army and EPA selected a final remedy to remove MEC from the surface (among other things), but this will take at least 10 years or more to implement at the current pace, due to weather and endangered species challenges associated with conducting vegetation clearance activities in support of MEC removal.
	HI	PEARL HARBOR NAVAL COMPLEX	Currently on the Final NPL	Y	Department of Defense		Current Human Exposure Not Controlled	fish advisories ineffective. Consumption of contaminated fish continues despite signs, fencing. Unless fish monitoring shows fish within acceptable levels, even if a remedy is implemented by 2015, for example, levels of contaminants in fish could persist for years, making exposures still not under control. 2020 Under Control date would be at the first Five Year Review. RAA 12 VI issues also need to be addressed, but likley before 2020	7/27/2017	6/30/2030 12:00:00 AM	The site-wide Human Exposure Control Status at the Pearl Harbor Naval Complex is Not Under Control due to continued consumption of contaminated fish, despite a fish advisory and access controls. Subsistence fishermen continue to enter the facility in remote, hard to control areas, and catch and consume contaminated fish. In addition, servicemen are often seen fishing off of facility docks and from the shoreline, often right next to signs. As part of the Navy's harbor sediment RI, EPA has asked the Navy to reassess the fish advisory in terms of ineffective access controls as well as additional fish monitoring. Field work to catch fish and analyze sediment is underway. Once these studies are complete, EPA can determine appropriate control measures.

10	WA	JACKSON PARK HOUSING COMPLEX (USNAVY)	Currently on the Final NPL	Y	US Navy		Current Human Exposure Not Controlled	UXO exposure not controlled yet, although some non-UXO areas have been cleaned up	9/21/2016	2/4/2019 12:00:00 AM	The Jackson Park Housing Complex/Naval Hospital Bremerton Superfund site is considered Human Exposure Not Under Control because discarded military munitions were found in the Housing Complex and Hospital areas, and in the intertidal zone and sediments of adjacent Ostrich Bay. In addition, a failed groundwater remedy for the Operable Unit 1 Benzene Release Area does not meet groundwater cleanup criteria for the site and continues to discharge TPH and benzene into the surface waters of Ostrich Bay. Surface clearance of discarded munitions has been completed at the Housing Complex and the Hospital but not in Ostrich Bay. Although the Navy has posted signs on its side of Ostrich Bay, no current Institutional Controls or educational programs exist for the general public use of Ostrich Bay, and use of the bay is not restricted. The primary routes of exposure of concern to EPA are recreational use of Ostrich Bay and the recurring commercial sea cucumber harvests conducted in the bay. EPA is concerned that commercial harvesters and recreational users could come into contact with and be harmed by munitions.

Region	State	Site Name	NPL Status	Federal Facility Flag	Federal Agency
02	PR	ATLANTIC FLEET WEAPONS TRAINING AREA	Currently on the Final NPL	Y	
04	FL	TYNDALL AIR FORCE BASE	Currently on the Final NPL	Y	Department of Defense
08	UT	HILL AIR FORCE BASE	Currently on the Final NPL	Y	US Air Force
09	CA	FORT ORD	Currently on the Final NPL	Y	Department of Defense
	HI	PEARL HARBOR NAVAL COMPLEX	Currently on the Final NPL	Y	Department of Defense

Brac Name	EI Human Exp Survey Result	HE Justification Change Description
	Current Human Exposure Not Controlled	see exposure pathway description
	Current Human Exposure Not Controlled	
	Current Human Exposure Not Controlled	Basewide Indoor Air Sampling is ongoing. Vapor removal systems have been installed and based on the results of future sampling more vapor removal systems may be installed.
BRAC 2	Current Human Exposure Not Controlled	Despite fencing, signage, police patrols, community mailings, briefings in schools, and removal actions to protect population from exposure to unexploded ordnance across over 8000 acres, it is difficult to keep trespassers out of an area surrounded by 11 miles of fencing because some areas remote. Exposure could result in great bodily harm or death.
	Current Human Exposure Not Controlled	fish advisories ineffective. Consumption of contaminated fish continues despite signs, fencing. Unless fish monitoring shows fish within acceptable levels, even if a remedy is implemented by 2015, for example, levels of contaminants in fish could persist for years, making exposures still not under control. 2020 Under Control date would be at the first Five Year Review. RAA 12 VI issues also need to be addressed, but likley before 2020

HE Last Review Date	HE Estimated Exposure Control Date
9/30/2016	9/30/2025 12:00:00 AM
11/23/2016	9/30/2017 12:00:00 AM
6/1/2017	9/30/2018 12:00:00 AM
5/24/2017	9/30/2020 12:00:00 AM
7/27/2017	6/30/2030 12:00:00 AM

HE Pathway
There is insufficient information to determine the site-wide human exposure status at the Atlantic Fleet Weapons Training Area - Vieques Superfund Site. The Atlantic Fleet Weapons Training Area - Vieques, includes certain areas of the island of Vieques and nearby waters that have become contaminated primarily by United States Department of Defense (DoD) activities. From the 1940s until 2003, the US Navy administered lands on both the western and eastern ends of Vieques Island. The lands were used for military training and operations (ship-to-shore gun fire, air-to-ground bombing by naval aircraft, Marine amphibious landing, or combinations), and to store munitions for Atlantic Fleet training. Extensive amounts of unexploded ordnance and remnants of exploded ordnance have been identified in the range areas of Vieques, and in the surrounding waters. The Navy is currently conducting a removal of all surface munitions and explosives of concern in the impact area in east Vieques. This action needs to be completed before a comprehensive study to evaluate the nature and extent of the contamination can be performed. Currently, hazardous substances that may be present at the site have not been fully characterized, but may include mercury, lead, copper, magnesium, lithium, perchlorate, TNT, napalm, depleted uranium, PCBs, solvents, and pesticides. As soon as the time critical removal action of unexploded ordnance is complete, the Navy will conduct an RI/FS to define the nature and extent of the contamination. EPA ensures community participation throughout the remedial process by meeting with residents and affected stakeholders, issuing public notices and updating fact sheets. A site profile has been established on the EPA website to keep the community informed of recent progress at the site. Additionally, an EPA Community Involvement Coordinator is assigned to the site and can address specific community concerns as they arise
The Tyndall Air Foce Base is considered Human Exposure Not Under Control. DDT is reported in fish and sediments throughout Shoal Point Bayou. The levels of contaminants to which humans are exposed do not fall within levels designated as safe by EPA. The 2002 RI for Shoal Point Bayou concluded that consumption of fish and shellfish from the Bayou should not be permitted in order to be protective of human health at the 1 x 10-4 risk level. Similarly, dermal contact with DDT in the Bayou was found to present an unacceptable risk to waders. It is reasonable to expect that people come into contact with contaminated media at this waste unit. Tyndall AFB representatives have informed EPA that private boats enter Shoal Point Bayou for recreational fishing and wading. There are no physical barriers to prevent public access by water or by land to the DDT contaminated media. EPA issued a RCRA 7003 imminent and substantial endangerment Order to the Air Force on November 21, 2007, to address base-wide contaminant conditions at Tyndall Air Force Base. The Order sets deadlines for Air Force development of enforceable schedules for cleanup activities. These activties will include early actions by the Air Force, such as improved warning signage and community outreach regarding fish consumption and wading hazards, to mitigate unacceptable exposures to contaminants at OT29 pending final cleanup of the Bayou.
The Hill Air Force Base Superfund site is considered "Current Human Exposure Not Under Control" because potential exposure to vapors from contaminated groundwater entering residences is still under investigation. The Air Force has developed a program to investigate as many as 2600 residences and install vapor extraction systems where needed to protect human health for the short term. Remedial actions are in place to address the contaminants in ground water, which will address the source of the vapors in the long term. There is an ongoing community outreach program at the Base.
The Fort Ord Superfund site is considered Human Exposure Not Under Control because trespassers can come into contact with munitions and explosives of concern (MEC), specifically in the 8000 acre impact range. As of April 2009, U.S. Army has installed fences throughout impacted areas, posted signs advising against entering the area, sent fact sheets about the site, and conducted briefings in local schools encouraging people not to enter the site, but trespassing continues, putting people in danger from contact with explosives. In 2008, the Army and EPA selected a final remedy to remove MEC from the surface (among other things), but this will take at least 10 years or more to implement at the current pace, due to weather and endangered species challenges associated with conducting vegetation clearance activities in support of MEC removal.
The site-wide Human Exposure Control Status at the Pearl Harbor Naval Complex is Not Under Control due to continued consumption of contaminated fish, despite a fish advisory and access controls. Subsistence fishermen continue to enter the facility in remote, hard to control areas, and catch and consume contaminated fish. In addition, servicemen are often seen fishing off of facility docks and from the shoreline, often right next to signs. As part of the Navy's harbor sediment RI, EPA has asked the Navy to reassess the fish advisory in terms of ineffective access controls as well as additional fish monitoring. Field work to catch fish and analyze sediment is underway. Once these studies are complete, EPA can determine appropriate control measures.

10	WA	JACKSON PARK HOUSING COMPLEX (USNAVY)	Currently on the Final NPL	Y	US Navy

	Current Human Exposure Not Controlled	UXO exposure not controlled yet, although some non-UXO areas have been cleaned up

9/21/2016	2/4/2019 12:00:00 AM

The Jackson Park Housing Complex/Naval Hospital Bremerton Superfund site is considered Human Exposure Not Under Control because discarded military munitions were found in the Housing Complex and Hospital areas, and in the intertidal zone and sediments of adjacent Ostrich Bay. In addition, a failed groundwater remedy for the Operable Unit 1 Benzene Release Area does not meet groundwater cleanup criteria for the site and continues to discharge TPH and benzene into the surface waters of Ostrich Bay. Surface clearance of discarded munitions has been completed at the Housing Complex and the Hospital but not in Ostrich Bay. Although the Navy has posted signs on its side of Ostrich Bay, no current Institutional Controls or educational programs exist for the general public use of Ostrich Bay, and use of the bay is not restricted. The primary routes of exposure of concern to EPA are recreational use of Ostrich Bay and the recurring commercial sea cucumber harvests conducted in the bay. EPA is concerned that commercial harvesters and recreational users could come into contact with and be harmed by munitions.

j

To: Burchette, John[Burchette.John@epa.gov]
Cc: Treimel, Ellen[Treimel.Ellen@epa.gov]
From: Bertrand, Charlotte[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F044D768E05842E1B75321FF6010E1B8-BERTRAND, CHARLOTTE]
Sent: Thur 7/27/2017 10:28:12 PM (UTC)
Subject: Re: EI-HENC Detailed 0727171820jb.xlsx

Terrific! Thanks!

Sent from my iPhone

On Jul 27, 2017, at 6:27 PM, Burchette, John <Burchette.John@epa.gov> wrote:

Charlotte,
Here you go (I was about halfway into it so I just finished it). Let me know if you need anything else.

Region	State	Site Name	NPL Status	Federal Facility Flag	Federal Agency	Brac Name
02	PR	ATLANTIC FLEET WEAPONS TRAINING AREA	Currently on the Final NPL	Y		
04	FL	TYNDALL AIR FORCE BASE	Currently on the Final NPL	Y	Department of Defense	
08	UT	HILL AIR FORCE BASE	Currently on the Final NPL	Y	US Air Force	
09	CA	FORT ORD	Currently on the Final NPL	Y	Department of Defense	BRAC 2

	HI	PEARL HARBOR NAVAL COMPLEX	Currently on the Final NPL	Y	Department of Defense	
10	WA	JACKSON PARK HOUSING COMPLEX (USNAVY)	Currently on the Final NPL	Y	US Navy	

<EI-HENC Detailed 0727171820jb.xlsx>

To: Herrera, Angeles[Herrera.Angeles@epa.gov]
Cc: Pang, Tiffanie[Pang.Tiffanie@epa.gov]; Bell-Anderson, Marie[Bell-Anderson.Marie@epa.gov]; Riveland, Nancy[Riveland.Nancy@epa.gov]; LINCOFF, MEILING[Lincoff.Meiling@epa.gov]; Ball, Harold[Ball.Harold@epa.gov]; Chesnutt, John[Chesnutt.John@epa.gov]; Dirscherl, Christopher[Dirscherl.Christopher@epa.gov]; Yo-Eco, Anabel[Yo-Eco.Anabel@epa.gov]; Gervais, Gregory[Gervais.Gregory@epa.gov]
From: Bertrand, Charlotte[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F044D768E05842E1B75321FF6010E1B8-BERTRAND, CHARLOTTE]
Sent: Tue 8/29/2017 10:32:25 PM (UTC)
Subject: Re: FY 2016 9R available funding - MUST BE Obligated by September 30

You are welcome - hope it helps!

Sent from my iPhone

On Aug 29, 2017, at 5:00 PM, Herrera, Angeles <Herrera.Angeles@epa.gov> wrote:

<image001.gif>
Yes. Thanks for the additional funding and everyone's efforts in making this happen.

From: Pang, Tiffanie
Sent: Tuesday, August 29, 2017 11:40 AM
To: Bell-Anderson, Marie <Bell-Anderson.Marie@epa.gov>
Cc: Herrera, Angeles <Herrera.Angeles@epa.gov>; Riveland, Nancy <Riveland.Nancy@epa.gov>; LINCOFF, MEILING <Lincoff.Meiling@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Chesnutt, John <Chesnutt.John@epa.gov>; Dirscherl, Christopher <Dirscherl.Christopher@epa.gov>; Yo-Eco, Anabel <Yo-Eco.Anabel@epa.gov>; Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>
Subject: RE: FY 2016 9R available funding - MUST BE Obligated by September 30

Thanks Marie! We will process the PRs immediately after Region 9 received the funds. Thanks again for everything!!!

Tiffanie Pang
U.S. Environmental Protection Agency, Region 9
Superfund Division
Program Management Office, SFD-2
Phone: (415) 972-3697
Email: pang.tiffanie@epa.gov

From: Bell-Anderson, Marie
Sent: Tuesday, August 29, 2017 11:33 AM
To: Pang, Tiffanie <Pang.Tiffanie@epa.gov>
Cc: Herrera, Angeles <Herrera.Angeles@epa.gov>; Riveland, Nancy <Riveland.Nancy@epa.gov>; LINCOFF, MEILING <Lincoff.Meiling@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Chesnutt, John <Chesnutt.John@epa.gov>; Dirscherl, Christopher <Dirscherl.Christopher@epa.gov>; Yo-Eco, Anabel <Yo-Eco.Anabel@epa.gov>; Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Bell-Anderson, Marie <Bell-Anderson.Marie@epa.gov>
Subject: RE: FY 2016 9R available funding - MUST BE Obligated by September 30

Hello Tiffanie. Thanks for the amounts and justifications for Region 9 additional funding needs. I will be processing an reprogramming for $50,000 under FY 2016 TD funding by Wednesday, Aug. 30. Please let me know if you have any concerns. Thanks.

From: Pang, Tiffanie
Sent: Tuesday, August 29, 2017 2:29 PM
To: Bell-Anderson, Marie <Bell-Anderson.Marie@epa.gov>
Cc: Herrera, Angeles <Herrera.Angeles@epa.gov>; Riveland, Nancy <Riveland.Nancy@epa.gov>; LINCOFF, MEILING

<Lincoff.Meiling@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Chesnutt, John <Chesnutt.John@epa.gov>; Dirscherl, Christopher <Dirscherl.Christopher@epa.gov>; Yo-Eco, Anabel <Yo-Eco.Anabel@epa.gov>
Subject: RE: FY 2016 9R available funding - MUST BE Obligated by September 30
Importance: High

Hi Marie,

I have checked in with Angeles and the followings are Region 9's additional funding requests. Please let me know if you have any questions or need additional information. Thank you for your support!

Task Order	Site Name	Funding Needs	WP Capacity	Justification
16	Williams AFB	$24,000	$161,636.28	Additional funds need to support the ongoing revi of technical documents i FFA, as well as to suppo the dispute resolution process with technical analyses and overall pro support.
26	LLNL - Site 300	$6,000	$12,784.85	LLNL Site 300 has seve technically complex FYI both in FY17 and FY18 a vapor intrusion screeni level evaluation in proce that was identified as a priority in a current FYI Additional funds need to address two RI/FS revie (Building 850 Perchlorat and B865) and the Vapo Intrusion Screening Lev (VISL) evaluation.
25	Hunters Point	$20,000	$112,424.80	Extra contract support needed for critical radiat assessment work and ongoing time-critical cle work underway.

Tiffanie Pang
U.S. Environmental Protection Agency, Region 9
Superfund Division
Program Management Office, SFD-2
Phone: (415) 972-3697
Email: pang.tiffanie@epa.gov

From: Bell-Anderson, Marie
Sent: Wednesday, August 23, 2017 8:32 AM
To: Dalal, Pradip <Dalal.Pradip@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; DiCosmo, Nefertiti <dicosmo.nefertiti@epa.gov>; Faulk, Dennis <Faulk.Dennis@epa.gov>; Goldblum, Deborah

<Goldblum.Deborah@epa.gov>; Herrera, Angeles <Herrera.Angeles@epa.gov>; Hirsh, Steven <Hirsh.Steven@epa.gov>; Juett, Lynn <Juett.Lynn@epa.gov>; Law, Preston <law.preston@epa.gov>; Leclerc, Russell <Leclerc.Russell@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Lombardo, Ginny <Lombardo.Ginny@epa.gov>; Loughlin, Anni <loughlin.anni@epa.gov>; Meyer, John <Meyer.John@epa.gov>; Pocze, Doug <Pocze.Doug@epa.gov>; Rigger, Don <Rigger.Don@epa.gov>; Sanchez, Carlos <sanchez.carlos@epa.gov>; Short, Thomas <short.thomas@epa.gov>; Stites, Rob <Stites.Rob@epa.gov>
Cc: Aguilar, Mark <Aguilar.Mark@epa.gov>; Bishop, Debbie <Bishop.Debbie@epa.gov>; Buonopane, Joan <Buonopane.Joan@epa.gov>; Chambers, Carlene <Chambers.Carlene@epa.gov>; Dunbar, Danielle <dunbar.danielle@epa.gov>; Field, Jeff <Field.Jeff@epa.gov>; Gee, Jo <Gee.Jo@epa.gov>; Johnson, Jennifer S. <Johnson.JenniferS@epa.gov>; Kershner, Lynne <Kershner.Lynne@epa.gov>; McEnery, Courtney <mcenery.courtney@epa.gov>; Rodriguez, Mandi <Rodriguez.Mandi@epa.gov>; Ruiz, Maryanne <ruiz.maryanne@epa.gov>; Saunders, Vince <saunders.vince@epa.gov>; Singletary, Antoinette <Singletary.Antoinette@epa.gov>; Stites, Rob <Stites.Rob@epa.gov>; Tzhone, Stephen <tzhone.stephen@epa.gov>; Whitley, Charlotte <whitley.charlotte@epa.gov>; Yo-Eco, Anabel <Yo-Eco.Anabel@epa.gov>; Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Bell-Anderson, Marie <Bell-Anderson.Marie@epa.gov>
Subject: FY 2016 9R available funding - MUST BE Obligated by September 30

Hello All,

We a **small amount of funding available** that **MUST BE obligated by September 30**. If you have a contract or grant vehicle that could use some additional funding, please **let us know asap**. Please provide the amount and justification for the additional funding.

Please let me know of any concerns. Thanks.

FYI my last name (Bell-Anderson) will be updated in the EPA Directory/Outlook email effective Jan. 10

Marie A. Bell-Anderson
Program Analyst
Environmental Protection Agency
Office of Land and Emergency Management
Federal Facilities Restoration and Reuse Office – 5106R
(202) 564-0775 Desk - (571) 229-0325 Work Mobile - (202) 564-0771 - Fax

Mailing Address
USEPA Headquarters
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 5106R (FFRRO)
Washington, DC 20460
Courier Address:
Ronald Reagan Building
1300 Pennsylvania Ave., N.W.
Rm # 71156
Washington, DC 20004

The best use of LIFE is LOVE
The best expression of LOVE is TIME
The best TIME to LOVE is NOW.

Message

From: Bertrand, Charlotte [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F044D768E05842E1B75321FF6010E1B8-BERTRAND, CHARLOTTE]
Sent: 6/22/2017 3:41:42 PM
To: Burchette, John [Burchette.John@epa.gov]; Cooke, Maryt [Cooke.Maryt@epa.gov]; Young, Dianna [Young.Dianna@epa.gov]
Subject: RE: Edwards

Great – thanks!

From: Burchette, John
Sent: Thursday, June 22, 2017 11:21 AM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

Charlotte,
Take a look at bullet 3. There may be a typo there w AF elevates to AF.
I pasted below some older (now outdated notes I had on the timeline of events). I also pasted a screenshot of the agreed upon issue and rec from the 2012 5-YR that the Region and State approved from my understanding

Timeline of events for Edwards PCE Dispute

1/2014- Consistent with the issues and recommendations in the agreed upon 2012 5-year review, the Air Force submitted a draft Explanation of Significant Differences (ESD) for the South Air Force Research Laboratory to add the California Maximum Contaminant Level for perchlorate, changing the value that was used in the 2008 ROD. However, the draft ESD also proposed to change the toxicity value for PCE from the California Office of Environmental Health Hazard Assessment value to the IRIS value issued by EPA in 2012.
8/22/2014- California Department of Toxic Substance Control presents and issue for dispute resolution.
- "very specifically whether the United States Environmental Protection Agency's (EPA's) Office of Solid Waste and Emergency Response (OSWER) guidance, in particular, OSWER Directive 9285.7-53 (2003) should be interpreted to require the Tier I Integrated Risk Information System (IRIS) toxicity criteria (or values) to be used by the project management team (the Remedial Project Managers (RPMs) from both the military and regulatory agencies, with assistance of their support professionals) when they exist, regardless of the existence of Tier II and Tier III levels for any given contaminant of concern (COC)."
- "This is a fundamental change in approach, and results in a much smaller area within the VICB than established by the ROD."
2/4/2015- The Air Force submitted the Explanation of Significant Differences (ESD) to the Senior Executive Committee (SEC). The Dispute Resolution Committee (DRC) agreed to elevate the dispute to the SEC via the subject submittal by 4 Feb 2015 :
State of California revised issues (different than in 8/22/2014 letter):
-1. "How should toxicity criteria be established, or more specifically, which toxicity criteria should be utilized for risk determination and action levels (where applicable or relevant and appropriate requirements are unavailable)?"

-2. "Should a decision to increase the toxicity value from the previous value agreed upon in the approved Record of Decision (ROD) be considered a fundamental change to the remedy so that it should be noticed and explained through a ROD amendment and not an ESD?"

EPA Region 9 position paper supporting California

-1. "EPA Region 9 Support statement of California Position 1: "The OEHHA toxicity value for PCE should be used because it is more stringent and EPA Region 9 has a longstanding agreement with the State of California to use the more stringent toxicity value at Superfund sites within California."

-2. "EPA Region 9 believes that changing a more stringent toxicity value previously selected in a ROD to a less stringent toxicity value should be done through a ROD Amendment, not an ESD."

6/9/2015- Regional Administrator decision.

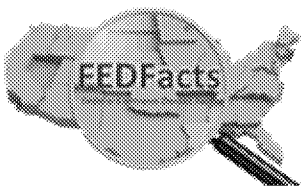
1: on the process issue, requires a ROD Amendment to be used as the document to change the PCE toxicity value. The Regional Administrator's decision states that the suggested change represents a fundamental change to the original decision and will require the document to go through a public comment period.

2: Did not address the proposed change of the PCE toxicity value.

Issues/Recommendations				
OU(s) without Issues/Recommendations Identified in the Five-Year Review:				
Sites without Issues/recommendations are not identified in the Five-Year Review.				
Issues and Recommendations Identified in the Five-Year Review:				
OU(s): South AFRL OU4 and OU9 (Sites 37, 133, 139, and Site 321)	Issue Category: Monitoring			
	Issue: California primary Maximum Contaminant Level (pMCL) for perchlorate adopted in October 2007, 4 times lower than the containment level selected in Record of Decision (ROD).			
	Recommendation: Prepare an Explanation of Significant Differences (ESD) to adopt the CA pMCL as the perchlorate level to be contained inside the South AFRL Containment Zone (CZ).			
Affect Current Protectiveness	Affect Future Protectiveness	Implementing Party	Oversight Party	Milestone Date
No	Yes	Federal Facility	EPA	Prior to 2017
OU(s): South AFRL OU4 and OU9 (Sites 37, 133, 139, and 321)	Issue Category: Monitoring			
	Issue: Based on recent updates to the Integrated Risk Information System (IRIS) database, trichloroethene (TCE) is more toxic and tetrachloroethene (PCE) is less toxic than considered in CA Office of Environmental Human and Ecological Assessment (OEHHA) database used to develop indoor air vapor mitigation levels (IAVMLs) selected in ROD.			
	Recommendation: In ESD, update IAVMLs for PCE and TCE to incorporate use of the updated toxicity criteria.			
Affect Current Protectiveness	Affect Future Protectiveness	Implementing Party	Oversight Party	Milestone Date
No	No	Federal Facility	EPA	Prior to 2017

John Burchette
Office of Land and Emergency Management
Federal Facilities Restoration and Reuse Office – 5106R
Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460
Phone: 202-564-3338
Cell: Ex. 6 Personal Privacy (PP)

Learn about Federal Facility Cleanups in your area:



From: Bertrand, Charlotte
Sent: Thursday, June 22, 2017 11:11 AM

To: Burchette, John <Burchette.John@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

I've put this slide in the FFRRO general (ugh, the timeline looks bad). Do you have edits?

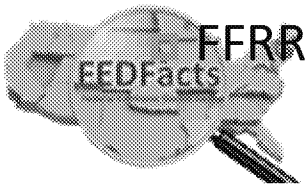
- Background
  - AF and State disagree on toxicity value for PCE (IRIS vs. State va
  - 2014: State initiated dispute when AF proposed to adopt new
  - 2015: AF elevates R9 decision to AF
  - 2016: OECA DAA defers/returns dispute to R9 for 15 months so
    should reconvene to discuss the California effort *(ARAR creatio*
    dispute and are further encouraged to continue discussions in
    prior to February 15, 2017"
- Current Status
  - SEC has not meet – R9 rescheduling June 26th meeting to Au
  - State has not proposed rule, earliest expected date is Augus
- Recommendation
  - FFRRO recommends no more deferrals, incorporate IRIS or S

From: Burchette, John
Sent: Thursday, June 22, 2017 11:09 AM
To: Cooke, Maryt <Cooke.Maryt@epa.gov>; Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

The one thing I can't anticipate is how this one may be influenced by high level political appointees. Seems very straightforward with the guidance etc. we have in place.

John Burchette
Office of Land and Emergency Management
Federal Facilities Restoration and Reuse Office – 5106R
Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania Avenue N. W.
Washington, DC 20460
Phone: 202-564-3398
Cell: Ex. 6 Personal Privacy (PP)

Learn about Federal Facility Cleanups in your area:



From: Cooke, Maryt
Sent: Thursday, June 22, 2017 11:07 AM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Burchette, John <Burchette.John@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

This is crazy –

I spoke to John this AM . . . the contradiction between this PCE issue and the TI waiver at the same site is mind boggling. The region may have to be able to account for the disconnect if the AF pushes it.

From: Bertrand, Charlotte
Sent: Thursday, June 22, 2017 11:00 AM
To: Burchette, John <Burchette.John@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

UGH!!!! This has gone on too long.

From: Burchette, John
Sent: Thursday, June 22, 2017 10:57 AM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

Sent the Shari letter in a separate email…5-year review was Sept 2012

412TH Test Wing
Edwards Air Force Base, California

Environmental Restoration Program

South AFRL First Five-Year Review Report
(Sites 37, 133, 120, and 321)

Air Force Research Laboratory
Detachment 7
Operable Units 4 and 9
Edwards AFB, California

Final

September 2012

John Burchette
Office of Land and Emergency Management
Federal Facilities Restoration and Reuse Office – 5106R
Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460
Phone: 202-564-3338
Cell: Ex. 6 Personal Privacy (PP)

Learn about Federal Facility Cleanups in your area:

From: Bertrand, Charlotte
Sent: Thursday, June 22, 2017 10:50 AM
To: Burchette, John <Burchette.John@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

Do you happen to have the Shari Wilson memo to Jared handy?

From: Burchette, John
Sent: Thursday, June 22, 2017 10:49 AM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: RE: Edwards

I want to say 2012?

John Burchette
Office of Land and Emergency Management
Federal Facilities Restoration and Reuse Office – 5106R
Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Washington, DC 20460
Phone: 202-564-3338
Cell: Ex. 6 Personal Privacy (PP)

Learn about Federal Facility Cleanups in your area:

From: Bertrand, Charlotte
Sent: Thursday, June 22, 2017 10:44 AM
To: Burchette, John <Burchette.John@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>
Subject: Edwards

Do you remember what year the five year review was in that AF proposed to adopt the IRIS value for PCE?

Message

From: Burneson, Eric [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2CACB9A8D49F49AF80531E9E2CCB9018-EBURNESO]
Sent: 3/1/2018 10:55:06 PM
To: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Subject: RE: Edwards AFB ROD amendment -
Attachments: Perchlorate OLEM Issue 3-1-18.docx

Here is a revised per our discussion.

From: Mclain, Jennifer
Sent: Thursday, March 01, 2018 3:45 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: FW: Edwards AFB ROD amendment -

I will stop by re: this and the one-pager

From: Forsgren, Lee
Sent: Thursday, March 01, 2018 3:19 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: Edwards AFB ROD amendment -

Let's talk about this.

Sent from my iPhone

Begin forwarded message:

> **From:** "Bodine, Susan" <bodine.susan@epa.gov>
> **Date:** March 1, 2018 at 2:34:50 PM EST
> **To:** "Forsgren, Lee" <Forsgren.Lee@epa.gov>, "Ross, David P" <ross.davidp@epa.gov>
> **Cc:** "Cook, Steven" <cook.steven@epa.gov>
> **Subject: RE: Edwards AFB ROD amendment -**
>
> Jim Woolford is handling.
> I would also could talk to Steve Cook.
>
> I don't know if OLEM is aware of OW's or ORD's work. I asked my Federal Facilities Enforcement people to reach out to OW and ORD, but I don't think they have done so. Who should I direct them to?
>
> ---
>
> **From:** Forsgren, Lee
> **Sent:** Thursday, March 1, 2018 2:11 PM
> **To:** Bodine, Susan <bodine.susan@epa.gov>; Ross, David P <ross.davidp@epa.gov>
> **Subject:** RE: Edwards AFB ROD amendment -
>
> Susan,

I completely agree. That is especially true if we are going to make a determination not to regulate Perchlorate. Who should we talk to at OLEM on the matter? Kell?

Lee

From: Bodine, Susan
Sent: Thursday, March 1, 2018 1:56 PM
To: Ross, David P <ross.davidp@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>
Subject: Edwards AFB ROD amendment -

Air Force proposes to amend a Superfund Record of Decision to adopt to 6 ppm CA MCL for perchlorate based on a determination made in 2012 that the ROD cleanup level of 24 ppm was not protective of human health because it exceeded a hazard index of 1. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP) OW's current drinking water advisory is 15 ppb and that is the number SF currently uses. But you have work underway.

They also propose to change the TCE number to reflect a new (lower) IRIS value for TCE. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

They also want to change the PCE number since there is a new IRIS value that is higher than their number.

The NCP says we don't change cleanup levels to reflect new standards unless the old level is no longer protective.

Susan

Appointment

From: Olson, Daniel [Olson.Daniel@epa.gov]
Sent: 1/25/2017 1:34:26 PM
To: Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]
CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]

Subject: BBDR Model Status
Attachments: Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment
Location: DCRoomEast2339/DC-ICC-OW-OGWDW; Ex. 6 Personal Privacy (PP)

Start: 1/31/2017 8:00:00 PM
End: 1/31/2017 9:00:00 PM
Show Time As: Busy

Recurrence: Weekly
every Tuesday from 3:00 PM to 4:00 PM

Appointment

To: Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]

CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]

Location: DCRoomEast2339/DC-ICC-OW-OGWDW; Ex. 6 Personal Privacy (PP)

Start: 1/31/2017 8:00:00 PM
End: 1/31/2017 9:00:00 PM
Show Time As: Busy

Recurrence: (none)

Please find attached 1) draft technical direction for continued support from ORNL/Teresa Leavens, and 2) January 26 briefing for Jen Mclain (OGWDW Acting Deputy Director) on model revision next steps (based on outcome of 1/23 meeting). PLEASE USE THE ATTACHED "BRIEFING BBDR Model Next Steps 01-25-17_lc (003)." SORRY FOR THE CONFUSION, and 3) "Appendix B" discussing variation in renal clearance.

Standing meeting on BBDR model status. Not all people can make all meetings but it is the best time for most people.

Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

Appointment

To: Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]
CC: Cantilli, Robert [Cantilli.Robert@epa.gov]

Location: 2400 east; Ex. 6 Personal Privacy (PP)

Start: 2/14/2017 8:00:00 PM
End: 2/14/2017 9:00:00 PM
Show Time As: Busy

Recurrence: (none)

Room change to 2400 east.

Attached please find:

1. Draft peer review report. We just received and have not had the opportunity to review. Consider this a close hold until we review and discuss internally.

2. A write up of the additional three NHANES correlation runs -

   - Since TSH levels in pregnant and non-pregnant women are statistically the same, run a combined set of correlations for TSH
   - Run a correlation between fT4 and TSH in pregnant women
   - Combine data on urinary perchlorate, nitrate and thiocyanate for pregnant and non-pregnant women and evaluate for correlation in these combined data

Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

Appointment

To: Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]

CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]

Location: DCRoomEast2339/DC-ICC-OW-OGWDW; Ex. 6 Personal Privacy (PP)

Start: 3/21/2017 7:00:00 PM
End: 3/21/2017 8:00:00 PM
Show Time As: Busy

Recurrence: (none)

Discussion topics:

- ? Initial distribution estimates for urinary clearance (Dustin, attached)
- ? MOA literature review for hypothyroxinemia in the first trimester (Ahmed)
- ? ?Plan B? statistical approach (Jessica/Ahmed)
- ? NHANES summary statistics and previous correlation between low iodine and fT4 (Jessica)
- ? Overall status of model expansion (Paul)
- ? Other?

Attached is the revised version of the document Dustin shared last month. In the first 3 pages, this document shows our proposed strategy for estimating key model parameters that describe perchlorate, iodine, and T4 toxicokinetics and toxicodynamics. Recall that for the proof-of-concept, Dustin used synthetic data. He has now appended new pages to this document that show results obtained using actual data from the Greer et al. (2002) study that were provided by Dr. Gay Goodman.

Conference room: 2339 WJC East
Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

To: Christ, Lisa[Christ.Lisa@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Hafez, Ahmed[Hafez.Ahmed@epa.gov]; Helm, Erik[Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov[jeffrey.fisher@fda.hhs.gov]; kinetics@leavens.us[kinetics@leavens.us]; Miller, Gregory[Miller.Gregory@epa.gov]; Schlosser, Paul[Schlosser.Paul@epa.gov]; Kapraun, Dustin[Kapraun.Dustin@epa.gov]; Georges, Jessica[Georges.Jessica@epa.gov]; Noyes, Pamela[Noyes.Pamela@epa.gov]; Perkinson, Russ[Perkinson.Russ@epa.gov]
From: Olson, Daniel[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=D380E158EBEB40B7B844D85225FB82D8-DOLSON]
Sent: Wed 2/15/2017 2:03:33 PM (UTC)
Subject: Draft Weekly Update
Feb 15 Perchlorate Update DRAFT.docx

All,

Please find attached for your review the weekly update regarding expansion of the BBDR model and MCLG report. I received bullets from Greg and Ahmed. Please provide comments by 2 this afternoon so I can send the update to the workgroup and OW managers by COB today.

Thanks!

Dan

To: Olson, Daniel[Olson.Daniel@epa.gov]; Christ, Lisa[Christ.Lisa@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Hafez, Ahmed[Hafez.Ahmed@epa.gov]; Helm, Erik[Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov[jeffrey.fisher@fda.hhs.gov]; kinetics@leavens.us[kinetics@leavens.us]; Miller, Gregory[Miller.Gregory@epa.gov]; Kapraun, Dustin[Kapraun.Dustin@epa.gov]; Georges, Jessica[Georges.Jessica@epa.gov]; Noyes, Pamela[Noyes.Pamela@epa.gov]; Perkinson, Russ[Perkinson.Russ@epa.gov]
From: Schlosser, Paul[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: Wed 2/15/2017 2:47:37 PM (UTC)
Subject: RE: Draft Weekly Update
Feb 15 Perchlorate Update DRAFT.ps.docx

A couple of track-change edits in the attached.

-Paul

From: Olson, Daniel
Sent: Wednesday, February 15, 2017 9:04 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory <Miller.Gregory@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>
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To: Schlosser, Paul[Schlosser.Paul@epa.gov]; Olson, Daniel[Olson.Daniel@epa.gov]; Christ, Lisa[Christ.Lisa@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Hafez, Ahmed[Hafez.Ahmed@epa.gov]; Helm, Erik[Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov[jeffrey.fisher@fda.hhs.gov]; kinetics@leavens.us[kinetics@leavens.us]; Miller, Gregory[Miller.Gregory@epa.gov]; Georges, Jessica[Georges.Jessica@epa.gov]; Noyes, Pamela[Noyes.Pamela@epa.gov]; Perkinson, Russ[Perkinson.Russ@epa.gov]
From: Kapraun, Dustin[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3A53C151B92A472FBFB295ED5DF982A7-KAPRAUN, DU]
Sent: Wed 2/15/2017 2:56:18 PM (UTC)
Subject: RE: Draft Weekly Update
Feb 15 Perchlorate Update DRAFT ps dfk.docx

I've added one track-change edit to those Paul sent.

-Dustin

From: Schlosser, Paul
Sent: Wednesday, February 15, 2017 9:48 AM
To: Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory <Miller.Gregory@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>
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To: Olson, Daniel[Olson.Daniel@epa.gov]; Christ, Lisa[Christ.Lisa@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Schlosser, Paul[Schlosser.Paul@epa.gov]; Morozov, Viktor[Morozov.Viktor@epa.gov]
From: Kapraun, Dustin[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3A53C151B92A472FBFB295ED5DF982A7-KAPRAUN, DU]
Sent: Thur 4/27/2017 2:50:19 PM (UTC)
Subject: slides for presentation at ORD CoP Statistics
perchlorate_param_est_cop_stats_20170502.pdf

Dear Dan et al.,

I have attached a PDF that contains all the slides I'm planning to use for my presentation to ORD's Community of Practice for Statistics on Tuesday, May 2, at 2:00. Please review these and let me know if you have any questions, comments, or concerns.

Thanks!
Dustin

Dustin F. Kapraun, Ph.D.
Applied Mathematician
National Center for Environmental Assessment
US Environmental Protection Agency
109 T.W. Alexander Drive (B243-01)
Research Triangle Park, NC 27709

Office: B230G
Phone: 919.541.4045
Email: kapraun.dustin@epa.gov

Message

From: George, BJ [George.BJ@epa.gov]
Sent: 4/10/2017 1:33:14 PM
To: Community of Practice for Statistics [CoP-Statistics@epa.gov]
CC: Vandenberg, John [Vandenberg.John@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]; Davis, Allen [Davis.Allen@epa.gov]; Gift, Jeff [Gift.Jeff@epa.gov]; Hotchkiss, Andrew [Hotchkiss.Andrew@epa.gov]; Benson, William [Benson.William@epa.gov]; Holt, Kay [Holt.Kay@epa.gov]; Hines, Ronald [Hines.Ronald@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Townsend, Clifton [Townsend.Clifton@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; El Burai Felix, Alia [ElBuraiFelix.Alia@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Fegley, Robert [Fegley.Robert@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
Subject: HHRA BMDS slides posted & Dustin Kapraun our speaker May 2

Dear Community of Practice for Statistics:

Allen Davis' and **Jeff Gift's** Benchmark Dose Software slides are posted on our Meetings page
Ex. 6 Personal Privacy (PP) **John Vandenberg's** and **Annie Jarabek's** HHRA Research Program introduction slides are also posted there. These presentations are wonderful!

For our May 2 meeting, **Dustin Kapraun** (NCEA) will give a talk titled "From Data to Decisions: Estimating Physiological Parameters to Inform a Perchlorate MCLG." Please watch for an agenda message late April or early May. I will update the calendar invitation next.

Please forward this message to EPA colleagues who may be interested. If you were forwarded this message and would like to be included in our e-mail list, here is the link to sign up: http://www.nheerl.epa.gov/COP/subscribe.cfm.

B.J.

Barbara Jane George, PhD, PStat®
Leader, ORD Community of Practice for Statistics
Senior Science Advisor
Immediate Office, NHEERL, ORD, U.S. EPA
(919) 541-4551

From: George, BJ
Sent: Thursday, March 30, 2017 10:21 AM
To: Community of Practice for Statistics <CoP-Statistics@epa.gov>
Cc: Vandenberg, John <Vandenberg.John@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Gift, Jeff <Gift.Jeff@epa.gov>; Hotchkiss, Andrew <Hotchkiss.Andrew@epa.gov>; Benson, William <Benson.William@epa.gov>; Holt, Kay <Holt.Kay@epa.gov>; Hines, Ronald <Hines.Ronald@epa.gov>
Subject: Agenda for HHRA presentation April 4

Dear Community of Practice for Statistics:

For our April 4 meeting, **Allen Davis** and **Jeff Gift** (NCEA) will present "EPA's Benchmark Dose Software (BMDS) and Related Models and Methods for Dose-Response Analysis" in an overview of statistical tools developed by the Human Health Risk Assessment (HHRA) program. Drs. Davis and Gift will discuss statistical models for evaluation of dichotomous, nested dichotomous, continuous and categorical data currently available in BMDS. They will also preview

modules for time dependence, exposure-to-dose conversions, model averaging, Bayesian meta-regression of data from multiple epidemiological studies, and assessing the toxicological similarity of candidate mixtures to a reference mixture(s).

Please forward this message to EPA colleagues who may be interested. If you were forwarded this message and would like to be included in our e-mail list, here is the link to sign up: http://www.nheerl.epa.gov/COP/subscribe.cfm.

Our April meeting is Tuesday, April 4th at 2:00 PM Eastern in RTP's B-301 and by Webinar
Webinar informatio Ex. 6 Personal Privacy (PP) s
Conference lin Ex. 6 Personal Privacy (PP)
Code Ex. 6 Personal Privacy (PP)

B.J.

Barbara Jane George, PhD, PStat®
Leader, ORD Community of Practice for Statistics
Ex. 6 Personal Privacy (PP)
(919) 541-4551

Message

From: Evalenko, Sandy [Evalenko.Sandy@epa.gov]
Sent: 3/24/2017 2:21:23 PM
To: InteragencyReviews [InteragencyReviews@epa.gov]
CC: Johnson, Ann [Johnson.Ann@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Fegley, Robert [Fegley.Robert@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Gerstein, Arielle [gerstein.arielle@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Ruf, Christine [Ruf.Christine@epa.gov]
Subject: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"
Attachments: Perchlorate denial of petition Mar2017 dgo.docx

We appreciate the opportunity to comment on the HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition." OW has a few general and specific comments. The Specific comments are inserted in the text of the attached FRN. These are also saved in the Team room. I've copied the program staff on this email if you have questions.

Sandy

FINAL RULE:

Ex. 5 Deliberative Process (DP)

DENIAL OF PETITION:

Ex. 5 Deliberative Process (DP)

From: InteragencyReviews
Sent: Wednesday, March 22, 2017 2:54 PM
To: RSC Core <RSC_Core@epa.gov>; RSC Regions Core <RSC_Regions_Core@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>; Adamson, Joseph <adamson.joseph@epa.gov>; Corrales, Mark <Corrales.Mark@epa.gov>; Hessert, Aimee <Hessert.Aimee@epa.gov>; InteragencyReviews <InteragencyReviews@epa.gov>; Kime, Robin <Kime.Robin@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Rees, Sarah <rees.sarah@epa.gov>
Subject: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"
Importance: High

For comment by Noon Friday, 03/24.

These interagency review documents are deliberative and pre-decisional and may not be shared or discussed with anyone outside of the Executive Branch.

Attached for expedited EO 12866 / 13563 interagency review and comment are a final rule and a denial of petition notice from HHS/FDA entitled "***Indirect Food Additives: Polymers***" & "***Natural Resources Defense Council et al.; Denial of Food Additive Petition***."

Ex. 5 Deliberative Process (DP)

Note: The consumer advocacy organizations have sued FDA to address their petition, and FDA reached an agreement to take action on the petition by March 31, 2017.

Process Notes / Tips for Responding

There is no strict response format, however, to facilitate compilation of the Agency's comments, please:

- use "Track Changes" (i.e., redline/strikeout and comment 'bubbles') to directly insert comments into the file and
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If the Agency has a big stake in the outcome, or its response is extensive and/or potentially controversial, the lead office may draft a transmittal note for OP to use when submitting the comments to OMB.

Please submit comments via your Regulatory Steering Committee (RSC) Representative, or Regional Regulatory Contact (RRC), who should send them to the proxy mailbox, InteragencyReviews@epa.gov, or post them in the RSC Team Room.

RSC Reps and RRC's may follow this doclink->Notes Link

Stuart Miles-McLean | Interagency Review Coordinator
Office of Regulatory Policy & Management | Office of Policy | Office of the Administrator
202.564.6581 | 3512-U WJC North | Mail Code 1803 | 1200 Pennsylvania Avenue NW | Washington, DC 20460

Message

From: InteragencyReviews [InteragencyReviews@epa.gov]
Sent: 3/24/2017 6:39:36 PM
To: Fegley, Robert [Fegley.Robert@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]
CC: Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Gerstein, Arielle [gerstein.arielle@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Ruf, Christine [Ruf.Christine@epa.gov]; Foos, Brenda [Foos.Brenda@epa.gov]; InteragencyReviews [InteragencyReviews@epa.gov]; Adamson, Joseph [adamson.joseph@epa.gov]
Subject: RE: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"
Attachments: EPA Cmnts-Perchlorate denial of petition Mar2017.docx

Importance: High

Hi Bob and Lynn,

ORD, OW, and OCHP have provided comments on this action.

I merged OW's and OCHP's redline/strikeout comments in the attached file, but not ORD's. You provided editorial comments on some of the same language in your email (below), so I would very much appreciate it if ORD added its redline/strikeout comments directly to the file to ensure I do not somehow mishandle you input and then 'Reply All' so everyone is on the same page. (btw, Ann is out of the office today)

I am happy to include your introductory Comments 1, 2, & 3 in my transmittal note to OMB, but I would like to send just one set of mark-ups.

As you know, this is due to OMB today, so please respond as quickly as possible.

Thanks, Stuart

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Office of Regulatory Policy & Management | Office of Policy | Office of the Administrator
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==========

From: Fegley, Robert
Sent: Thursday, March 23, 2017 3:44 PM
To: InteragencyReviews <InteragencyReviews@epa.gov>
Cc: Flowers, Lynn <Flowers.Lynn@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
Subject: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"

Stuart et al. --

Thanks for the opportunity to review the FDA notice. We have no comments on the final rule file. However, For the response to the NRDC petition, ORD has one ***major*** comment that affects the text in two places (p. 37 and 41) and an additional comment regarding the purpose of EPA's recent peer review of the perchlorate modeling effort. I'd like to thank Lynn Flowers (ORD/OSP) for her review.

Ex. 5 Deliberative Process (DP)

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I will also post this response to the Team Room

Bob Fegley

Robert Fegley, Chief
Program Support Staff
Office of Science Policy/ORD/EPA
Washington DC

202/564-6786

From: InteragencyReviews
Sent: Wednesday, March 22, 2017 2:54 PM
To: RSC Core <RSC_Core@epa.gov>; RSC Regions Core <RSC_Regions_Core@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>; Adamson, Joseph <adamson.joseph@epa.gov>; Corrales, Mark <Corrales.Mark@epa.gov>; Hessert, Aimee <Hessert.Aimee@epa.gov>; InteragencyReviews <InteragencyReviews@epa.gov>; Kime, Robin <Kime.Robin@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Rees, Sarah <rees.sarah@epa.gov>
Subject: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"
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Sent: 3/24/2017 7:31:13 PM
To: InteragencyReviews [InteragencyReviews@epa.gov]; Fegley, Robert [Fegley.Robert@epa.gov]
CC: Evalenko, Sandy [Evalenko.Sandy@epa.gov]; Johnson, Ann [Johnson.Ann@epa.gov]; Flaharty, Stephanie [Flaharty.Stephanie@epa.gov]; Gerstein, Arielle [gerstein.arielle@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Ruf, Christine [Ruf.Christine@epa.gov]; Foos, Brenda [Foos.Brenda@epa.gov]; Adamson, Joseph [adamson.joseph@epa.gov]
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Attachments: EPA Cmnts-Perchlorate denial of petition Mar2017.docx

Here you go. I kept the same file name. I used comment bubbles to merge my comments in two places (pg 37 and 41). I also called myself "author" for consistency. My comment 2 below is no longer applicable. OW edited that part and their edits are much better than mine.

Thanks!

Lynn

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Policy
US EPA
Washington, DC
202-564-6293

From: InteragencyReviews
Sent: Friday, March 24, 2017 2:40 PM
To: Fegley, Robert <Fegley.Robert@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>
Cc: Evalenko, Sandy <Evalenko.Sandy@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Gerstein, Arielle <gerstein.arielle@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Ruf, Christine <Ruf.Christine@epa.gov>; Foos, Brenda <Foos.Brenda@epa.gov>; InteragencyReviews <InteragencyReviews@epa.gov>; Adamson, Joseph <adamson.joseph@epa.gov>
Subject: RE: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"
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Office of Regulatory Policy & Management | Office of Policy | Office of the Administrator
202.564.6581 | 3512-U WJC North | Mail Code 1803 | 1200 Pennsylvania Avenue NW | Washington, DC 20460

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Sent: Thursday, March 23, 2017 3:44 PM
To: InteragencyReviews <InteragencyReviews@epa.gov>
Cc: Flowers, Lynn <Flowers.Lynn@epa.gov>; Evalenko, Sandy <Evalenko.Sandy@epa.gov>
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I will also post this response to the Team Room

Bob Fegley

Robert Fegley, Chief
Program Support Staff
Office of Science Policy/ORD/EPA
Washington DC

202/564-6786

From: InteragencyReviews
Sent: Wednesday, March 22, 2017 2:54 PM
To: RSC Core <RSC_Core@epa.gov>; RSC Regions Core <RSC_Regions_Core@epa.gov>
Cc: Johnson, Ann <Johnson.Ann@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>; Adamson, Joseph <adamson.joseph@epa.gov>; Corrales, Mark <Corrales.Mark@epa.gov>; Hessert, Aimee <Hessert.Aimee@epa.gov>; InteragencyReviews <InteragencyReviews@epa.gov>; Kime, Robin <Kime.Robin@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Nickerson, William <Nickerson.William@epa.gov>; Rees, Sarah <rees.sarah@epa.gov>
Subject: RSC Distribution: Action Item - HHS/FDA FRM and Notice for Expedited EPA Review: "Indirect Food Additives: Polymers" & "Natural Resources Defense Council et al.; Denial of Food Additive Petition"
Importance: High

For comment by Noon Friday, 03/24.

These interagency review documents are deliberative and pre-decisional and may not be shared or discussed with anyone outside of the Executive Branch.

Attached for expedited EO 12866 / 13563 interagency review and comment are a final rule and a denial of petition notice from HHS/FDA entitled "***Indirect Food Additives: Polymers***" & "***Natural Resources Defense Council et al.; Denial of Food Additive Petition***."

Ex. 5 Deliberative Process (DP)

Note: The consumer advocacy organizations have sued FDA to address their petition, and FDA reached an agreement to take action on the petition by March 31, 2017.

Process Notes / Tips for Responding

There is no strict response format, however, to facilitate compilation of the Agency's comments, please:

- use "Track Changes" (i.e., redline/strikeout and comment 'bubbles') to directly insert comments into the file and
- for general comments/concerns/observations, add them to a new blank page inserted at the beginning of the file.

In this way, the Agency's comments travel together – reducing the risk of confusion.

Comments do not require documented management approval, but should represent the views of the commenting AA-ship / RA-ship.

Typically an AA-ship / RA-ship with subject matter expertise takes the lead and coordinates the preparation of the Agency's response when an interagency review gives rise to comments from multiple offices. If no office volunteers to take the lead, OP may

still call on the commenting offices to work together to reconcile and compile their comments in order to ensure the commenters' input is not misinterpreted or misconstrued.

If the Agency has a big stake in the outcome, or its response is extensive and/or potentially controversial, the lead office may draft a transmittal note for OP to use when submitting the comments to OMB.

Please submit comments via your Regulatory Steering Committee (RSC) Representative, or Regional Regulatory Contact (RRC), who should send them to the proxy mailbox, InteragencyReviews@epa.gov, or post them in the RSC Team Room.

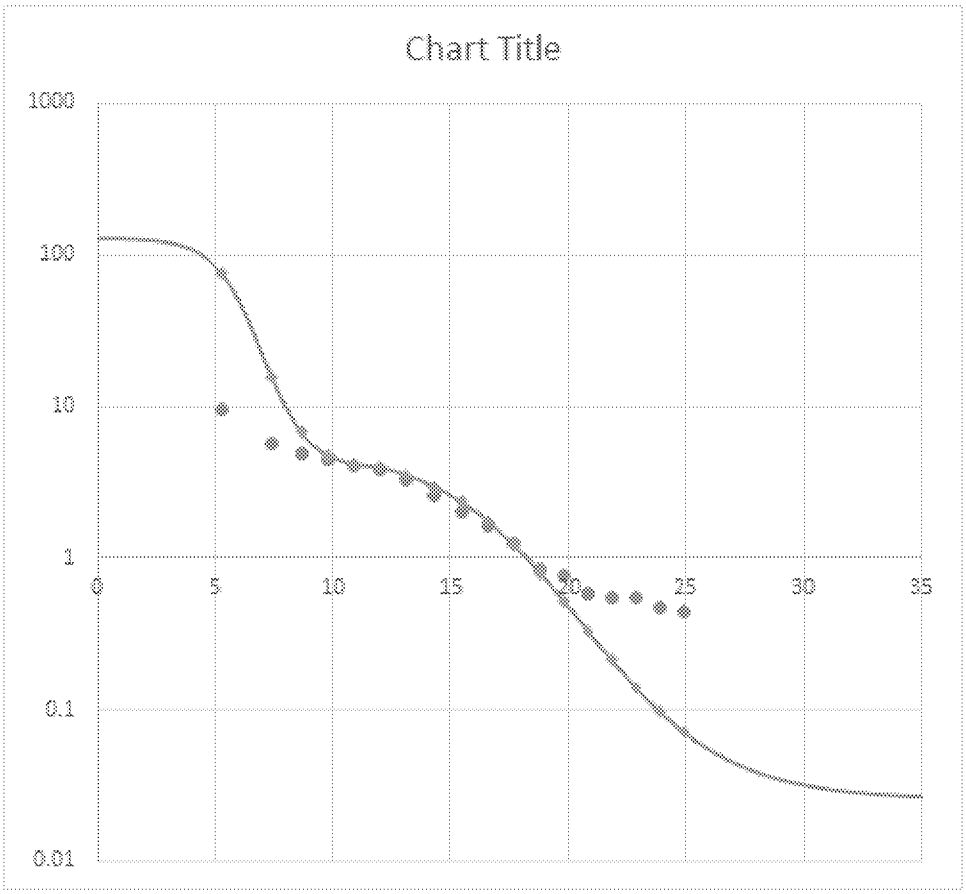
RSC Reps and RRC's may follow this doclink->Notes Link

Stuart Miles-McLean | Interagency Review Coordinator
Office of Regulatory Policy & Management | Office of Policy | Office of the Administrator
202.564.6581 | 3512-U WJC North | Mail Code 1803 | 1200 Pennsylvania Avenue NW | Washington, DC 20460

Message

From: Schlosser, Paul [Schlosser.Paul@epa.gov]
Sent: 3/21/2017 7:03:29 PM
To: Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; kinetics@leavens.us; Miller, Gregory [Miller.Gregory@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]
CC: Noyes, Pamela [Noyes.Pamela@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]
Subject: RE: BBDR Model Status

To discuss: TSH vs. fT4



-----Original Appointment-----
From: Olson, Daniel
Sent: Tuesday, March 21, 2017 12:14 PM
To: Christ, Lisa; Flowers, Lynn; Hafez, Ahmed; Helm, Erik; Jeff Fisher; kinetics@leavens.us; Miller, Gregory; Schlosser, Paul; Strong, Jamie; Kapraun, Dustin; Georges, Jessica
Cc: Noyes, Pamela; Cantilli, Robert; Gilbert, Mary E.
Subject: BBDR Model Status
When: Tuesday, March 21, 2017 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomEast2339/DC-ICC-OW-OGWDW; 866-299-3188 code 202 564 5239

Discussion topics:

- Initial distribution estimates for urinary clearance (Dustin, attached)
- MOA literature review for hypothyroxinemia in the first trimester (Ahmed)

- "Plan B" statistical approach (Jessica/Ahmed)
- NHANES summary statistics and previous correlation between low iodine and fT4 (Jessica)
- Overall status of model expansion (Paul)
- Other?

Attached is the revised version of the document Dustin shared last month. In the first 3 pages, this document shows our proposed strategy for estimating key model parameters that describe perchlorate, iodine, and T4 toxicokinetics and toxicodynamics. Recall that for the proof-of-concept, Dustin used synthetic data. He has now appended new pages to this document that show results obtained using actual data from the Greer et al. (2002) study that were provided by Dr. Gay Goodman.

Conference room: 2339 WJC East
Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)

Message

From: Schlosser, Paul [Schlosser.Paul@epa.gov]
Sent: 3/10/2017 3:11:49 PM
To: Jeff Fisher [Jeffrey.Fisher@fda.hhs.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Kapraun, Dustin [Kapraun.Dustin@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]; Noyes, Pamela [Noyes.Pamela@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Gilbert, Mary E. [Gilbert.Mary@epa.gov]; kinetics@leavens.us; Cantilli, Robert [Cantilli.Robert@epa.gov]
Subject: RE: Total serum iodine measurement in the Greer study

P.S. We have Hays and Solomon (already in HERO), but not DeGroot, citation below. I have to request HERO to buy the article.

-Paul

Degroot, L. J., Decostre, P., and Phair, R. (1971). A mathematical model of human iodine metabolism. J. Clin. Endocrinol. Metab. 32, 757–765.

From: Fisher, Jeffrey [mailto:Jeffrey.Fisher@fda.hhs.gov]
Sent: Friday, March 10, 2017 9:49 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; Gilbert, Mary E. <Gilbert.Mary@epa.gov>; kinetics@leavens.us; Cantilli, Robert <Cantilli.Robert@epa.gov>
Subject: RE: Total serum iodine measurement in the Greer study

Double check the our human model (Merrill). We did the experimental measurements of perchlorate in the Greer study and I thought we did iodide in serum. All the iodine reported by Gay was done using ashing, an old method for total iodine. In theory, perchlorate exposure increases the urinary excretion of iodide.

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, March 10, 2017 7:51 AM
To: Flowers, Lynn; Olson, Daniel; Christ, Lisa; Fisher, Jeffrey; Miller, Gregory; Kapraun, Dustin; Hafez, Ahmed; Perkinson, Russ; Noyes, Pamela; Helm, Erik; Gilbert, Mary E.; kinetics@leavens.us; Cantilli, Robert
Subject: RE: Total serum iodine measurement in the Greer study

Hi Lynn,

I am very appreciative that Gay has curated and shared these data for us. I don't want that to get lost.

The data that I had thought we would receive, and would be of value in estimating the urinary clearance constant for iodide, would be the free iodine in serum matched with urinary iodide excretion (UIE). From Gay's email, these are total serum iodine, which would include T4 and T3 (and rT3?). And in any case, without the UIE, we could not estimate the urinary clearance constant of iodide for the subjects. Inter-individual variation in that constant would impact estimation of variation in thyroidal iodide uptake, and the effect of perchlorate.

Free serum iodide might be estimated by subtracting the iodide associated with TT4 and TT3 in the subjects. Mean +/- SE for these are provided in the paper, for each subject, but ideally the data at each time point would be used (accounting for 4 iodide/T4 and 3/T3) to figure out how much is 'organified'.

So unfortunately, we can't really use this subset of the data in isolation from UIE and (preferably) individual TH levels at each time-point.

I'm not sure which way this will influence Dustin's analysis. On the one hand, some of the variation that's really due to variation in urinary clearance of iodine will effectively be attributed to variation in NIS-KM. On the other hand his analysis won't have to deal with the 'noise' due to variation in iodine clearance, unless we build that in using other data to estimate it.

Based on the general mechanism, I would have expected total urinary clearance to increase with perchlorate exposure, as thyroidal uptake is inhibited, but the clearance constant, ~ UIE/(free-serum-iodide), should not. But on face value the comment in Gay's last paragraph makes sense.

-Paul

From: Flowers, Lynn
Sent: Friday, March 10, 2017 4:23 AM
To: Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Jeff Fisher <Jeffrey.Fisher@fda.hhs.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; Gilbert, Mary E. <Gilbert.Mary@epa.gov>; kinetics@leavens.us; Cantilli, Robert <Cantilli.Robert@epa.gov>
Subject: Fwd: Total serum iodine measurement in the Greer study

Please see below and attached file.

Sent from my iPhone

Begin forwarded message:

From: "Gay Goodman" <ggoodman@hhrr.com>
Date: March 10, 2017 at 4:02:52 AM EST
To: "'Flowers, Lynn'" <Flowers.Lynn@epa.gov>
Subject: Total serum iodine measurement in the Greer study

Dear Lynn,

Serum was analyzed for total iodine only in the 24 subjects (12 M, 12 F) in the main study. Attached is an Excel file containing the serum total iodine data (by event) for the 12 female subjects in the main study.

The serum total iodine measurements were performed in the Braverman lab. In a subsequent email message I will provide you with information on how to cite these data properly.

Note that free iodine in serum was not measured, although it was supposed to be measured. I would have liked to rectify this omission but it was not possible to do so.

Another indicator of iodine status is urinary iodine excretion (UIE). In our conversation I also mentioned the UIE data but may not have been sufficiently clear about distinguishing the serum total iodine data from the UIE data. There are several challenges to analyzing the UIE data, including its possible dependence on perchlorate ingestion. In the published paper I will address the various issues surrounding the interpretation of the UIE data but do not think it would be wise to use the data beforehand.

Best regards,
Gay Goodman, PhD, DABT

Phone: 206-284-7436

From: Flowers, Lynn [mailto:Flowers.Lynn@epa.gov]
Sent: Wednesday, March 08, 2017 6:19 AM
To: Gay Goodman
Subject:

Dear Dr. Goodman:
Thanks again for the insightful conversation. It would be great to have the information that you kindly offered if it is not too much trouble.
To summarize – it is the summary data on blood iodine vs. urinary levels (mean, median, range) that would be helpful to have. As I recall, you were offering combined M and F data. That would be great. Female only would be perfect!
Thanks for your consideration.
Lynn

Lynn Flowers, PhD, DABT
Associate Director for Science
Office of Science Policy
US EPA
Washington, DC
202-564-6293

Message

From: Flowers, Lynn [Flowers.Lynn@epa.gov]
Sent: 2/28/2017 11:12:50 AM
To: Christ, Lisa [Christ.Lisa@epa.gov]
Subject: Re: BBDR Model Status

I hope to pay attention to this today. I have been back and forth with voice messages with Gay Goodman and we had to cancel one planned time to talk. Trying again early this afternoon Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP) Interesting infighting story re: industry influence Ex. 5 Deliberative Process (DP) Ex. 5 Deliberative Process (DP)

Sent from my iPhone

On Feb 27, 2017, at 12:59 PM, Christ, Lisa <Christ.Lisa@epa.gov> wrote:

Hi Lynn,
I wondered if you had a chance to look at the clarifying questions from Paul? In addition to what Paul teed- up, he and Jeff previously suggested the following:

- Ex. 5 Deliberative Process (DP)
- Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Lisa

From: Schlosser, Paul
Sent: Thursday, February 23, 2017 10:06 AM
To: Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; kinetics@leavens.us; Miller, Gregory <Miller.Gregory@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>; jeffrey.fisher@fda.hhs.gov
Cc: Cantilli, Robert <Cantilli.Robert@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>
Subject: RE: BBDR Model Status

Attached is my full set of clarifying questions, including the larger item in the email earlier this morning. I need to review the Pearce et al. (2016) paper, but have other responsibilities in the moment.

-Paul

From: Schlosser, Paul
Sent: Wednesday, February 22, 2017 4:09 PM
To: Olson, Daniel <Olson.Daniel@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; kinetics@leavens.us; Miller, Gregory <Miller.Gregory@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>; jeffrey.fisher@fda.hhs.gov
Cc: Cantilli, Robert <Cantilli.Robert@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>
Subject: RE: BBDR Model Status

See attached.

I've finished going through the report, up to p. 80. After that the report has specific/editorial comments.

In the attached I've tried to capture the key comments, and things that stood out in the individual comments, that were *not* captured in the summary. I may have lost track of the summary by the end, but I was trying to get all the unique comments.

Text in black/purple are reviewer comments on my paraphrasing. Red is my response/thoughts.

Purple are the things I flagged for clarification... maybe a couple more than desired.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

I will collect the purple items, and the 3 papers for which we'd like the underlying data, into a set of 'clarifying questions' to be sent tomorrow morning.

-Paul

-----Original Appointment-----
From: Olson, Daniel
Sent: Wednesday, January 25, 2017 8:34 AM
To: Olson, Daniel; Christ, Lisa; Flowers, Lynn; Hafez, Ahmed; Helm, Erik; kinetics@leavens.us; Miller, Gregory; Schlosser, Paul; Strong, Jamie; Kapraun, Dustin; Georges, Jessica; jeffrey.fisher@fda.hhs.gov
Cc: Cantilli, Robert; Noyes, Pamela
Subject: BBDR Model Status
When: Tuesday, February 21, 2017 3:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoom East 2123; Ex. 6 Personal Privacy (PP)

Room change to 2123 east.

Today's discussion topics:

- <!--[if !supportLists]--><!--[endif]-->Status of activities
- <!--[if !supportLists]--><!--[endif]-->Do we have (additional) clarifying questions for peer reviewers?
    - <!--[if !supportLists]--><!--[endif]-->Can we ask the clinicians if there is a standard reference used in the US for first trimester reference intervals for TSH, fT4, T4, T3, and hCG in healthy women?
    - <!--[if !supportLists]--><!--[endif]-->Can the clinicians identify what they consider the best of more recent literature characterizing TH regulation in pregnancy, particularly first trimester.

    - <!--[if !supportLists]--><!--[endif]-->Also in non-pregnant women of childbearing age, so the model can be parameterized for the start of pregnancy
- <!--[if !supportLists]--><!--[endif]-->Thyroid expertise – Mary Gilbert? Pearce or Leung?
- <!--[if !supportLists]--><!--[endif]-->Include a discussion in the report on the key physiological parameters
- <!--[if !supportLists]--><!--[endif]-->Decision on how to use the hX reference range
- <!--[if !supportLists]--><!--[endif]-->Probabilistic modeling? (Use parameter ranges/distributions to predict distributions of outputs?)

Call-in number: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)
<Carifying questions.docx>

Message

From: Olson, Daniel [Olson.Daniel@epa.gov]
Sent: 2/22/2017 8:01:19 PM
To: Christ, Lisa [Christ.Lisa@epa.gov]; Perkinson, Russ [Perkinson.Russ@epa.gov]
Subject: Science Advisor Memo on Selection Procedures
Attachments: Memorandum to File OSA-OW Meeting to discuss peer reviewers, Final.docx

FYI – Below are directions on how address selection procedures for the second panel. The first is an excerpt from the OSA memo to Phil. The second is an excerpt from Russ's meeting summary.

OSA memo -

> "OW will provide a list of the final proposed peer reviewers for the second panel to OSA and the Science Advisor designees will determine whether to hold a meeting with OW and the contractor to discuss any conflict of interest or appearance of a loss of impartiality related concerns regarding those reviewers."

Russ's meeting summary –

> "For the second panel, they indicated we'd not need to come back to OSA with the same level of detail if we draw from the same interim list of names as were presented in the Sept 30 FRN, perhaps needing just a memo from us. If the panel #2 interim reviewers vary slightly from that list (i.e., we add a name or two from Versar's pool of possible reviewers), I took it that we'd have to provide OSA with some information on any additional reviewers not on the interim list for panel #1, and perhaps would need a very brief meeting. But, I understood the process could still be more streamlined than needed for this briefing."

From: Perkinson, Russ
Sent: Tuesday, November 01, 2016 1:12 PM
To: Olson, Daniel <Olson.Daniel@epa.gov>
Subject: FW: A request -- approval to move forward

FYI

From: O'Farrell, Thomas
Sent: Tuesday, November 01, 2016 1:09 PM
To: Oshida, Phil <Oshida.Phil@epa.gov>
Cc: Greene, Mary <greene.mary@epa.gov>; Grifo, Francesca <Grifo.Francesca@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>
Subject: Re: A request -- approval to move forward

Phil and Russ,

Please find the attached meeting summary from last week's meeting regarding the final list of peer reviewers for the upcoming perchlorate model peer review (panel 1). Thank you.

Tom O'Farrell
ORD/OSA

From: Oshida, Phil
Sent: Tuesday, November 1, 2016 12:43:17 PM
To: O'Farrell, Thomas

Cc: Greene, Mary; Grifo, Francesca; Perkinson, Russ
Subject: A request -- approval to move forward

November 1, 2016

Tom,

I was impressed by the simplicity and efficiency of our meeting on Thursday, October 27 to seek approval of the reviewers for "our" Perchlorate BBDR Model.

As you know, we are hoping that OSA will very quickly let us know whether we have approval of the reviewers. It is imperative that we move forward expeditiously with the peer review process to meet our very tight, court ordered deadlines.

We were hoping for OSA's response yesterday. Is there a possibility that we can receive OSA's response today?

Thanks for considering this request.

-Phil-

Phil Oshida S Associate Director S Standards and Risk Management Division S Office of Ground Water and Drinking Water S Office of Water S U.S. EPA S 202.564.6594

To: Olson, Daniel[Olson.Daniel@epa.gov]; Christ, Lisa[Christ.Lisa@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Hafez, Ahmed[Hafez.Ahmed@epa.gov]; Helm, Erik[Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov[jeffrey.fisher@fda.hhs.gov]; kinetics@leavens.us[kinetics@leavens.us]; Miller, Gregory[Miller.Gregory@epa.gov]; Kapraun, Dustin[Kapraun.Dustin@epa.gov]; Georges, Jessica[Georges.Jessica@epa.gov]; Noyes, Pamela[Noyes.Pamela@epa.gov]; Perkinson, Russ[Perkinson.Russ@epa.gov]
From: Schlosser, Paul[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: Wed 2/22/2017 2:57:32 PM (UTC)
Subject: RE: Draft Perchlorate Weekly Update
Feb 22 Perchlorate Update DRAFT.ps.docx

A couple of small edits in copy attached, as track changes.

This morning I emailed authors of two papers, Horton et al. (2015) and Mortensen et al. (2016), that Jeff and I both thought would have good data, to ask if they would share the underlying data. Also there are 3 studies by Leung and/or Pearce that we have identified to ask for the data, but that will go as part of the 'clarifying questions'.

Also I've emailed Jon Sobus, NERL, to ask about urine and creatinine flow/output, including variability, to help in interpreting the biomarker data. There are a couple of studies showing correlation between perchlorate, thiocyanate, and nitrate in urine. I've also asked Jon if that might be an artifact of variation in urine flow or creatinine excretion. I think that if the 'denominator' used to normalize these measures increases or decreases, then the resulting concentrations or ratios will go up and down together, even if they aren't actually correlated.

-Paul

From: Olson, Daniel
Sent: Wednesday, February 22, 2017 8:45 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; jeffrey.fisher@fda.hhs.gov; kinetics@leavens.us; Miller, Gregory <Miller.Gregory@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>
Subject: Draft Perchlorate Weekly Update

All,

Please find attached for your review the weekly update regarding expansion of the BBDR model and MCLG report to early pregnancy. I received bullets from Greg and Ahmed. Please provide comments by 2 this afternoon so I can send the update to the workgroup and OW managers by COB today.

Thanks!

Dan

To: Christ, Lisa[Christ.Lisa@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Hafez, Ahmed[Hafez.Ahmed@epa.gov]; Helm, Erik[Helm.Erik@epa.gov]; jeffrey.fisher@fda.hhs.gov[jeffrey.fisher@fda.hhs.gov]; kinetics@leavens.us[kinetics@leavens.us]; Miller, Gregory[Miller.Gregory@epa.gov]; Schlosser, Paul[Schlosser.Paul@epa.gov]; Kapraun, Dustin[Kapraun.Dustin@epa.gov]; Georges, Jessica[Georges.Jessica@epa.gov]; Noyes, Pamela[Noyes.Pamela@epa.gov]; Perkinson, Russ[Perkinson.Russ@epa.gov]
From: Olson, Daniel[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=D380E158EBEB40B7B844D85225FB82D8-DOLSON]
Sent: Wed 2/22/2017 1:44:58 PM (UTC)
Subject: Draft Perchlorate Weekly Update
Feb 22 Perchlorate Update DRAFT.ps.docx

All,

Please find attached for your review the weekly update regarding expansion of the BBDR model and MCLG report to early pregnancy. I received bullets from Greg and Ahmed. Please provide comments by 2 this afternoon so I can send the update to the workgroup and OW managers by COB today.

Thanks!

Dan

Appointment

From: George, BJ [George.BJ@epa.gov]
Sent: 4/10/2017 1:33:57 PM
To: George, BJ [George.BJ@epa.gov]; Community of Practice for Statistics [CoP-Statistics@epa.gov]; Weaver, Anne [weaver.anne@epa.gov]; Ward-Caviness, Cavin [ward-caviness.cavin@epa.gov]; Neale, Anne [Neale.Anne@epa.gov]; Hagan, Nicole [Hagan.Nicole@epa.gov]; Garcia, Val [Garcia.Val@epa.gov]; Collins, Barbara [Collins.Barbara@epa.gov]; Suarez, Danielle [Suarez.Danielle@epa.gov]; Kirk, Andrea [Kirk.Andrea@epa.gov]; Weyer, Erica [weyer.erica@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]; Davis, Allen [Davis.Allen@epa.gov]; Gift, Jeff [Gift.Jeff@epa.gov]; Hotchkiss, Andrew [Hotchkiss.Andrew@epa.gov]; Benson, William [Benson.William@epa.gov]; Holt, Kay [Holt.Kay@epa.gov]; Hines, Ronald [Hines.Ronald@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Olson, Daniel [Olson.Daniel@epa.gov]; Townsend, Clifton [Townsend.Clifton@epa.gov]; Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]; Helm, Erik [Helm.Erik@epa.gov]; Georges, Jessica [Georges.Jessica@epa.gov]; Hafez, Ahmed [Hafez.Ahmed@epa.gov]; El Burai Felix, Alia [ElBuraiFelix.Alia@epa.gov]; Miller, Gregory [Miller.Gregory@epa.gov]; Strong, Jamie [Strong.Jamie@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; Cantilli, Robert [Cantilli.Robert@epa.gov]; Fegley, Robert [Fegley.Robert@epa.gov]; Christ, Lisa [Christ.Lisa@epa.gov]
CC: Sallam, Mohamed [sallam.mohamed@epa.gov]; Wu, Jianyong [wu.jianyong@epa.gov]; Saranjampour, Parichehr [saranjampour.parichehr@epa.gov]

Subject: Community of Practice for Statistics monthly meetings - February through June 2017
Location: in-person in RTP's B-301 or by webinar (information below)

Start: 5/2/2017 6:00:00 PM
End: 5/2/2017 7:00:00 PM
Show Time As: Tentative

Recurrence: Monthly
the first Tuesday of every 1 month(s) from 2:00 PM to 3:00 PM

Dustin Kapraun (NCEA) will give a talk titled **From Data to Decisions: Estimating Physiological Parameters to Inform a Perchlorate MCLG**. Please watch for an agenda message late April or early May.

Abstract: How can mathematical and statistical models help us to determine a Maximum Contaminant Level Goal (MCLG) for a chemical? By integrating such models using Bayesian methods, we obtained distributional estimates of four key physiological parameters required for a biologically-based dose response (BBDR) model for perchlorate. We begin this presentation with background on perchlorate and the BBDR modeling component of the perchlorate MCLG project, an NCEA and Office of Water collaboration. We then describe the models, data, and methods we used to obtain distributional estimates of the four key physiological parameters, which govern perchlorate and iodine kinetics in humans. This overview of a Bayesian parameter estimation approach based on Markov chain Monte Carlo (MCMC) methods will appeal to researchers with an interest in quantifying uncertainty in model parameters, model outputs, or model inputs.

You may attend our ORD Community of Practice for Statistics meeting in person in **RTP's B-301** or join in by conference call and webinar:

Conference call information: Ex. 6 Personal Privacy (PP)
Code: Ex. 6 Personal Privacy (PP)
Webinar information: Ex. 6 Personal Privacy (PP)

Community of Practice for Statistics website Ex. 6 Personal Privacy (PP)

(Please note that our August through December meetings are in a separate recurring invitation.)

Message

From: Tucker, Nicole [Tucker.Nicole@epa.gov]
Sent: 9/8/2017 7:59:01 PM
To: Huff, Lisa [Huff.Lisa@epa.gov]
CC: Christ, Lisa [Christ.Lisa@epa.gov]; Wadlington, Christina [Wadlington.Christina@epa.gov]; Albert, Ryan [Albert.Ryan@epa.gov]
Subject: FW: 9/21/17 ADVANCE NOTIFICATION - Hines et al. Use of AEP and AOP frameworks to integrated human health and ecological endpoints for cumulative risk assessment; perchlorate case study
Attachments: AEP_AOP_EST_r2.docx; ATT00001.htm; Fact_Sheet_AEP_AOP_CRA_Case_Study_Perchlorate_revision.docx; ATT00002.htm

Hi Lisa,
I was wondering if anyone in TAB would be interested in reviewing the attached manuscript? This manuscript discuss how the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks can be used to organize and evaluate exposure and dose response data across multiple species and endpoints. The authors present a case study using perchlorate.
ORD is interested in a policy review. Comments on policy are requested by Tuesday, September 19th. Please let me know if anyone would be interested in reviewing. Thank you Lisa.
-Nicole Tucker

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

From: Emerson, Vanessa
Sent: Thursday, September 07, 2017 6:46 AM
To: Strong, Jamie <Strong.Jamie@epa.gov>; Gallagher, Kathryn <Gallagher.Kathryn@epa.gov>; Balasa, Kate <balasa.kate@epa.gov>; Braverman, Carole <braverman.carole@epa.gov>; Corona, Joel <Corona.Joel@epa.gov>; Metchis, Karen <Metchis.Karen@epa.gov>; Ohanian, Edward <Ohanian.Edward@epa.gov>; Reiley, Mary <Reiley.Mary@epa.gov>; Smith, Lameka <Smith.Lameka@epa.gov>; Soares, Barbara <soares.barbara@epa.gov>; Tucker, Nicole <Tucker.Nicole@epa.gov>; Weinstock, Larry <Weinstock.Larry@epa.gov>; Zahreddine, Phil <Zahreddine.Phil@epa.gov>
Subject: Due: 9/21/17 ADVANCE NOTIFICATION - Hines et al. Use of AEP and AOP frameworks to integrated human health and ecological endpoints for cumulative risk assessment; perchlorate case study

Good morning,

Please find attached a manuscript for review. Comments are requested by September 21st. No response will be taken as a sign of no concern.

Thank you,
Vanessa

From: Ohanian, Edward
Sent: Thursday, September 7, 2017 6:17 AM
To: Emerson, Vanessa <emerson.vanessa@epa.gov>

Subject: Fwd: Deadline 9/21/17 ADVANCE NOTIFICATION - Hines et al. Use of AEP and AOP frameworks to integrated human health and ecological endpoints for cumulative risk assessment; perchlorate case study

Please handle. High optics for OW. Thx. Ed

Edward V. Ohanian, Ph.D.
Associate Director for Science
USEPA/Office of Water (MC: 4301T)
(202) 566-1117 (Voice)
(202) 566-0441(Fax)

Begin forwarded message:

> **From:** "Bahadori, Tina" <Bahadori.Tina@epa.gov>
> **To:** "Ohanian, Edward" <Ohanian.Edward@epa.gov>
> **Cc:** "D'Amico, Louis" <DAmico.Louis@epa.gov>, "Lavoie, Emma" <Lavoie.Emma@epa.gov>, "Jones, Samantha" <Jones.Samantha@epa.gov>
> **Subject: Deadline 9/21/17 ADVANCE NOTIFICATION - Hines et al. Use of AEP and AOP frameworks to integrated human health and ecological endpoints for cumulative risk assessment; perchlorate case study**
>
> Dear Ed,
>
> A multidisciplinary ORD team has produced a manuscript entitled, "The Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks facilitate the integration of human health and ecological endpoints for Cumulative Risk Assessment (CRA)." This study was performed under the auspices of the Human Health Risk Assessment National Program (HHRA 6.1) and used a computational modeling approach to integrate human health and ecological indicator to inform risk assessment. This study was motivated by program office needs for improved approaches for cumulative risk assessment. The manuscript is targeted for submission to *Environmental Science and Technology*.
>
> Given OW's interest in cumulative risk assessment and the use of perchlorate as the case study, we wanted to bring this manuscript to your attention and ask that you review it for potential policy implications to your office. **If as you review the this paper, you run across any show-stoppers please let me know by no later than Thursday, September 21, 2017.**
>
> To facilitate review, in addition to the manuscript, a one-page manuscript information sheet is also attached.
>
> I look forward to hearing back from you. Please let me know if you need additional information.
>
> With warm regards,
>
> Tina
>
> ==========
> **Tina Bahadori, Sc.D.**
> **Director, National Center for Environmental Assessment (EPA/ORD/NCEA)**
> **National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)**
> PYS-11622; 1200 Pennsylvania Avenue, NW, MC 8601P, Washington, DC 20460
> phone: 703-347-0283; mobi Ex. 6 Personal Privacy (PP) mail: Bahadori.Tina@epa.gov

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 3/1/2018 8:27:35 PM
To: Forsgren, Lee [Forsgren.Lee@epa.gov]
Subject: RE: Edwards AFB ROD amendment -

OK. Eric and I are meeting on perchlorate with all of the OD's and Barry Breen on Monday.

From: Forsgren, Lee
Sent: Thursday, March 01, 2018 3:19 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: Edwards AFB ROD amendment -

Let's talk about this.

Sent from my iPhone

Begin forwarded message:

> **From:** "Bodine, Susan" <bodine.susan@epa.gov>
> **Date:** March 1, 2018 at 2:34:50 PM EST
> **To:** "Forsgren, Lee" <Forsgren.Lee@epa.gov>, "Ross, David P" <ross.davidp@epa.gov>
> **Cc:** "Cook, Steven" <cook.steven@epa.gov>
> **Subject: RE: Edwards AFB ROD amendment -**
>
> Jim Woolford is handling.
> I would also could talk to Steve Cook.
>
> I don't know if OLEM is aware of OW's or ORD's work. I asked my Federal Facilities Enforcement people to reach out to OW and ORD, but I don't think they have done so. Who should I direct them to?
>
> ---
>
> **From:** Forsgren, Lee
> **Sent:** Thursday, March 1, 2018 2:11 PM
> **To:** Bodine, Susan <bodine.susan@epa.gov>; Ross, David P <ross.davidp@epa.gov>
> **Subject:** RE: Edwards AFB ROD amendment -
>
> Susan,
>
> I completely agree. That is especially true if we are going to make a determination not to regulate Perchlorate. Who should we talk to at OLEM on the matter? Kell?
>
> Lee
>
> ---
>
> **From:** Bodine, Susan
> **Sent:** Thursday, March 1, 2018 1:56 PM
> **To:** Ross, David P <ross.davidp@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>
> **Subject:** Edwards AFB ROD amendment -

Air Force proposes to amend a Superfund Record of Decision to adopt to 6 ppm CA MCL for perchlorate based on a determination made in 2012 that the ROD cleanup level of 24 ppm was not protective of human health because it exceeded a hazard index of 1. There was political pressure from Boxer at the time to agree to CA's number.

I am worried about precedent if the Superfund program is saying 24 ppm is not protective. OW's current drinking water advisory is 15 ppb and that is the number SF currently uses. But you have work underway.

They also propose to change the TCE number to reflect a new (lower) IRIS value for TCE. I am less concerned about that.

They also want to change the PCE number since there is a new IRIS value that is higher than their number.

The NCP says we don't change cleanup levels to reflect new standards unless the old level is no longer protective.

Susan

Appointment

From: Bodine, Susan [bodine.susan@epa.gov]
Sent: 2/28/2019 3:59:56 PM
To: Bodine, Susan [bodine.susan@epa.gov]; Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Azad, Ava [Azad.Ava@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Wright, Peter [wright.peter@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Stoker, Michael B. [stoker.michael@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Cook, Steven [cook.steven@epa.gov]
CC: Seter, David [Seter.David@epa.gov]; Ball, Harold [Ball.Harold@epa.gov]; Herrera, Angeles [Herrera.Angeles@epa.gov]; Minor, Dustin [Minor.Dustin@epa.gov]; Fairbanks, Brianna [Fairbanks.Brianna@epa.gov]; Maldonado, Lewis [Maldonado.Lewis@epa.gov]; Burchette, John [Burchette.John@epa.gov]; Young, Dianna [Young.Dianna@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Openchowski, Charles [openchowski.charles@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Woolford, James [Woolford.James@epa.gov]; Anderson, RobinM [Anderson.RobinM@epa.gov]; Johnson, SusanA [Johnson.SusanA@epa.gov]; Muller, Marie [MULLER.MARIE@EPA.GOV]; Stalcup, Dana [Stalcup.Dana@epa.gov]

Subject: Edwards AFB Dispute Pre-Brief, Call-in Number: Ex. 6 Personal Privacy (PP)
Attachments: Agenda - Edwards AFB Dispute 3.8.19 Meeting with EPA Administrator.docx; Final one pager _ Edwards Dispute - February 28 2019.docx; Final Edwards AFB FFA Dispute Briefing Paper for Acting Administrator Wheeler November 2018_.docx
Location: 3216 WJC-South

Start: 3/4/2019 10:00:00 PM
End: 3/4/2019 10:30:00 PM
Show Time As: Busy

Edwards Air Force Base – South Air Force Research Laboratory (AFRL), CA
CERCLA Federal Facility Agreement Formal Dispute Resolution
Briefing for Acting Administrator Wheeler
November 6, 2018

Purpose

Present options and associated policy implications for consideration to resolve the Edwards Air Force Base South AFRL CERCLA § 120 Federal Facility Agreement (FFA) dispute. The Air Force elevated this dispute to the EPA Administrator for resolution on January 31, 2018 in accordance with the FFA's dispute resolution process.

Posture of the Dispute

The parties agree the primary issue at dispute is whether to update a 2007 Record of Decision (ROD) to apply the 2012 EPA Integrated Risk Information System (IRIS) toxicity value for tetrachloroethene (PCE) to determine the appropriate vapor intrusion compliance boundary (VICB) calculation and the indoor air monitoring and compliance levels at South AFRL. The 2007 ROD selected the VICB and monitoring and compliance levels for PCE using a 1991 California Office of Environmental Health Hazard Assessment (OEHHA) toxicity value, as no IRIS value existed at the time of ROD signature. EPA established an IRIS value for PCE, which is less stringent than the 1991 OEHHA value, in 2012. OEHHA updated its PCE toxicity value in 2016 to a value slightly more stringent than its 1991 OEHHA value.

The Air Force would like to modify the ROD to apply the 2012 IRIS PCE toxicity value.

The California Department of Toxic Substances Control (DTSC) and Lahontan Regional Water Quality Control Board (Water Board) (together "California") would like to either retain the 1991 OEHHA value included in the ROD or apply the 2016 updated OEHHA value.

The dispute raises policy and precedent considerations. Resolution of the dispute will likely be a balancing of the countervailing policy considerations, described below, as they relate to the various options for resolution.

Background of the Dispute

Edwards Air Force Base (Edwards) is an active Air Force base on the National Priorities List (NPL). EPA, the Air Force, DTSC, and the Water Board are signatories to a 1990 CERCLA § 120 FFA for Edwards. The FFA establishes a framework for the investigation and cleanup, including a process for dispute resolution, beginning with informal dispute and ending with the EPA Administrator.

The FFA has the following process for dispute resolution: informal dispute, elevation to formal dispute for resolution by the Dispute Resolution Committee (Superfund Division Director-level), elevation to the Senior Executive Committee (Regional Administrator-level), and, finally, elevation to the EPA Administrator.

In 2007, the Air Force and EPA, with the concurrence of California, issued a ROD for South AFRL using, among other things, the OEHHA toxicity value for PCE. In 2014, the Air Force submitted a draft Explanation of Significant Differences (ESD) in response to issues identified in a 2012 five-year review.

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Specifically, the draft ESD proposed to update the Maximum Contaminant Level in groundwater for perchlorate to address a future protectiveness concern. The ESD also proposed to update the inhalation toxicity values for PCE and trichloroethylene (TCE).

In June 2014, California invoked informal dispute in response to the Air Force's proposal in the draft final ESD to modify the PCE toxicity value to apply the 2012 IRIS PCE toxicity value. The Region 9 Regional Administrator (RA) issued a decision in June 2015 stating that the change from the OEHHA value to the IRIS value would require a ROD amendment. The Air Force elevated the dispute to the Administrator in July 2015. In January 2016, at the request of the Office of the Administrator, the dispute was deferred for 15 months to allow California to update its PCE toxicity value,[1] and the dispute was referred to the Senior Executive Committee (RA level). On January 17, 2018, the Acting RA issued a decision stating that the PCE toxicity value in the 2007 ROD would not be modified as it remained protective, no site-specific factors supported modifying the value, and upholding cleanup levels selected in RODs provides certainty to the public, potentially responsible parties (PRPs), and parties interested in making use of CERCLA sites for redevelopment or reuse.

On January 31, 2018, the Air Force elevated the dispute to the Administrator requesting that the Administrator direct the Air Force to adopt EPA's 2012 PCE toxicity value at SAFRL.[2]

In the meantime, DTSC published a proposed Toxicity Criteria Rule[3] that establishes a process for selection of toxicity values, including a value for PCE. The public comment period for the rule closed, and DTSC submitted a final version of the rule to the Office of Administrative Law for review and publication in late July. DTSC promulgated the final rule on September 4, 2018, effective immediately. California intends to formally propose that EPA identify the rule to be an applicable or relevant and appropriate requirement (ARAR) at Superfund sites in California.

This issue is also the subject of a formal dispute at another operable unit (OU) at Edwards, and may arise again at other OUs at Edwards or at other Superfund sites in California.

Policy and Legal Considerations of this Dispute

1. EPA Guidance on Determining Which Toxicity Value to Apply in Superfund Risk Assessment

CERCLA § 121(d) requires that on-site remedial actions attain (or waive) federal or more stringent state ARARs. If a chemical-specific ARAR exists, it must be attained (or waived) upon completion of the remedial action. If no chemical-specific ARAR exists, a risk assessment is conducted to establish a risk-based value to be applied at the site for the chemical in question.

---

[1] OEHHA adopted its updated PCE inhalation unit risk value on September 8, 2016.

[2] The Air Force also requested that the Administrator: find that EPA Region 9 did not follow the FFA dispute procedures or the NCP by issuing a decision in response to the Air Force's 2015 elevation of this dispute stating that the Air Force's proposed change to the PCE toxicity value would require a ROD amendment; confirm that EPA must follow all FFA dispute resolution procedures, including time frames, absent all parties' agreement to a change; confirm or clarify EPA's guidance on the hierarchy of toxicity values to be used when multiple toxicity values exist for a given contaminant; and clarify the appropriate process for determining whether a change is "significant" (triggering an ESD) versus "fundamental" (triggering a ROD amendment). See Appendix 1 for further discussion of these additional requests and why EPA does not need to respond to these requests to resolve the dispute.

[3] The Notice of Proposed Rulemaking was issued on August 4, 2017.

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OSWER memorandum "Human Health Toxicity Values in Superfund Risk Assessment" (Hierarchy memorandum) discusses a hierarchy of toxicity values when carrying out a Superfund risk assessment.[4] The guidance provides three different tiers of toxicity values. Tier 1 is EPA's IRIS. Tier 2 is EPA's Provisional Peer Reviewed Toxicity Values, which are not relevant in this dispute. Tier 3 is "Other Toxicity Values." In this case, OEHHA's toxicity value is a Tier 3 value.

The Hierarchy memorandum indicates that IRIS is generally the preferred source of human health toxicity values. The memorandum states, "This revised hierarchy recognizes that EPA should use the best science available on which to base risk assessments. In general, if health assessment information is available in the Integrated Risk Information System . . . for the contaminant under evaluation, risk assessors normally need not search further for additional sources of information."

However, the memorandum also recognizes that there may be other sources of toxicological information: "IRIS is not the only source of toxicology information, and in some cases more recent, credible and relevant data may come to the Agency's attention. In particular, toxicological information other than in IRIS may be brought to the Agency by outside parties. Such information should be considered along with the data in IRIS in selecting toxicological values; ultimately, the Agency should evaluate risk based upon its best scientific judgment and consider all credible and relevant information available to it."

The Hierarchy memorandum further states, "EPA and state personnel may use and accept other technically sound approaches, either on their own initiative, or at the suggestion of potentially responsible parties, or other interested parties."

2. Consistency with CERCLA and the National Contingency Plan

Based in part in response to comments that PRPs need certainty in remedy selection, EPA stated in the preamble to the 1990 NCP, "Once a ROD is signed and a remedy chosen, EPA will not reopen that decision unless the new or modified requirement calls into question the protectiveness of the selected remedy. . . If ARARs were not frozen at . . . [the time of ROD signature], promulgation of a new or modified requirement could result in a reconsideration of the remedy and a restart of the lengthy design process, even if protectiveness is not compromised. This lack of certainty could adversely affect the operation of the CERCLA program, would be inconsistent with Congress' mandate to expeditiously cleanup sites and could adversely affect PRP negotiations, as noted by commenters." (55 Fed. Reg. at p. 8757, March 8, 1990).

The preamble states that, to address this matter of certainty in remedy selection, the final NCP includes the following provision: § 300.430(f)(1)(ii)(B): "On-site remedial actions selected in a ROD must attain those ARARs that are identified at the time of ROD signature or provide grounds for invoking a waiver under § 300.430(f)(1)(ii)(C)(3). (1) Requirements that are promulgated or modified after ROD signature must be attained (or waived) only when determined to be applicable or relevant and appropriate and necessary to ensure that the remedy is protective of human health and the environment."

In the current dispute, the OEHHA toxicity value(s) and the IRIS toxicity values are not ARARs.

Consistent with CERCLA and the NCP, a ROD is modified when a remedy is not protective; however, nothing in CERCLA or the NCP prohibits a ROD from being modified even if the current remedy is protective so long as the remedy, as modified, remains protective.

[4] OSWER Directives 9285.7-53 (2003), 9285.7-16 (1993), and 9285.7-86 (2013).

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In practice, EPA has modified RODs when the original remedy remained protective. For example, EPA recently proposed to modify a ROD at Portland Harbor, OR, at the request of a PRP. The PRP sought to have EPA apply a more recent, less stringent IRIS value for carcinogenic polycyclic aromatic hydrocarbons even though the cleanup level in the existing ROD is still considered protective. As with the Air Force position at Edwards, the Portland Harbor PRP sought to have EPA modify a protective remedy to apply a less stringent value. There are several key distinctions between Edwards and Portland Harbor:

- At Portland Harbor, the updated IRIS value was released three weeks after ROD signature where, at Edwards, the PCE IRIS value was released five years after ROD signature;
- At Portland Harbor, the comparison is between an older IRIS value and an updated IRIS value rather than a state value and an IRIS value as in the Edwards dispute;
- At Portland Harbor, the Oregon Department of Environmental Quality did not oppose the proposal to modify the ROD to apply the updated, less stringent IRIS value where, at Edwards, California is a party to the FFA and strongly opposes adopting IRIS; and
- Modification of the ROD to apply the updated IRIS value at Portland Harbor will result in an approximately $35 million cost savings in implementing the remedy while, at Edwards, the Air Force has stated that there is minimal cost difference at the affected Operable Units between applying the 1991 OEHHA value, the 2016 OEHHA value, and the IRIS value.

3. Comparison of the OEHHA and IRIS Approaches to Setting PCE Toxicity Values

The IRIS and OEHHA PCE values use the same underlying data and models. Both went through an extensive public comment period, received independent scientific peer review, and reflect reasoned scientific judgments. Both EPA and OEHHA developed values to protect the full population, including sensitive subpopulations.

In developing the IRIS value, EPA's National Center for Environmental Assessment (NCEA) concluded certain estimates of metabolism were too uncertain to be used with confidence. California OEHHA also recognized large uncertainties in those estimates, but chose a different way to reflect those estimates.

California OEHHA also chose to utilize estimates of human risk from a type of rat cancer that the IRIS assessment did not use (following the majority advice of the National Academy of Sciences (NAS) peer review panel). There was a minority group of scientists on the NAS panel who felt the rat cancers (a kind of leukemia) should be used in estimating human cancer risk. The IRIS assessment summary notes that higher cancer risks would result if one used that cancer type and that there were differing scientific views on that issue.

Finally, OEHHA took a different approach than did the IRIS assessment, by averaging the risk estimates from different types of laboratory animal cancers rather than the IRIS approach of using only the cancers in which it had the most confidence. The OEHHA approach resulted in an action level that is an order of magnitude lower (more stringent) than the level called for using the IRIS approach.

Although OEHHA's and EPA's review of the data resulted in different conclusions, both are reasoned scientific judgments reached on a complex dataset.

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4. Implications for the Superfund Program

Depending on the resolution, the outcome of this dispute could have national implications for the Superfund program.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

5. Implications for State Relations & Potential for Litigation

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

6. Cost Considerations

The NCP includes cost as a potential consideration to evaluate when considering whether a ROD modification is appropriate. As a policy matter, cost may be a reasonable factor to consider where a request is made to reopen or change a protective, selected remedy.

In this case, Air Force has stated that the cost difference for the South AFRL vapor intrusion remedy is minimal between application of the 1991 OEHHA value, the 2016 OEHHA value, and the 2012 IRIS value. The Air Force has stated that if it needed to construct additional buildings at Edwards within the South AFRL VICB, for which there are no current plans, the estimate for installing a passive vapor intrusion mitigation system per building is approximately $100,000.

Because the cost difference is minimal, this consideration is not included under each of the options below.

Dispute Resolution Options Under Consideration

Option 1. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Option 2. Ex. 5 Deliberative Process (DP)

Option 3. Ex. 5 Deliberative Process (DP)

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Options for Resolution

Option 1. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

California Position

Ex. 5 Deliberative Process (DP)

Air Force Position

Ex. 5 Deliberative Process (DP)

Key Policy/Legal Implications

Ex. 5 Deliberative Process (DP)

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Option 2. Ex. 5 Deliberative Process (DP)

California Position

Ex. 5 Deliberative Process (DP)

Air Force Position

Ex. 5 Deliberative Process (DP)

Key Policy/Legal Implications

Ex. 5 Deliberative Process (DP)

Option 3. Ex. 5 Deliberative Process (DP)

California Position

Ex. 5 Deliberative Process (DP)

Air Force Position

Ex. 5 Deliberative Process (DP)

Key Policy/Legal Implications

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

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Appendix 1: Air Force's requests from January 31, 2018 dispute elevation letter

In its January 31, 2018 dispute elevation letter, the Air Force requested that the Administrator:

1) direct the Air Force to adopt EPA's 2012 PCE toxicity value at SAFRL;
2) find that EPA Region 9 did not follow the FFA dispute procedures or the NCP by issuing a decision in response to the Air Force's 2015 elevation of this dispute stating that the Air Force's proposed change to the PCE toxicity value would require a ROD amendment;
3) confirm that EPA must follow all FFA dispute resolution procedures, including time frames, absent all parties' agreement to a change;
4) confirm or clarify EPA's guidance on the hierarchy of toxicity values to be used when multiple toxicity values exist for a given contaminant; and
5) clarify the appropriate process for determining whether a change is "significant" (triggering an ESD) versus "fundamental" (triggering a ROD amendment).

Ex. 5 Deliberative Process (DP)

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Appendix 2: Comparison of OEHHA versus IRIS outputs in the CERCLA risk range

The 2007 ROD set a Remedial Action Objective (RAO) of 10^{-6} as the appropriate cancer risk target for establishing cleanup levels and VICB for PCE.

At a 10^{-6} cancer risk target, applying the OEHHA toxicity value translates into a 2 µg/m3 concentration of PCE in indoor air, while applying the IRIS toxicity value translates into a 47 µg/m3 concentration of PCE in indoor air.

The boundaries of the geographic area identified in the 2007 ROD for vapor intrusion were based on the OEHHA toxicity value; those same boundaries would be deemed to correspond to a cancer risk target of $4.2x\ 10^{-8}$, if evaluated using the 2012 IRIS toxicity value. Likewise, the smaller geographic area proposed by the Air Force for vapor intrusion (also identified using 10^{-6} as the appropriate cancer risk target, but instead using the IRIS toxicity value) would be deemed to correspond to a cancer risk target of $2.3x\ 10^{-5}$, if evaluated using the OEHHA toxicity value.

OEHHA	
Inhalation Cancer Unit Risk (IUR) = $6.1x10^{-6}$ [1/(µg/m3)]	
Concentration in Indoor Air (µg/m3)	**Risk**
47	$2.3x10^{-5}$
2	$1x10^{-6}$

IRIS	
Inhalation Cancer Unit Risk (IUR) = $2.6x10^{-7}$ [1/(µg/m3)]	
Concentration in Indoor Air (µg/m3)	**Risk**
47	$1x10^{-6}$
2	$4.2x10^{-8}$

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Appendix 3: Chronology of the Dispute

- **August 30, 1990**: EPA listed Edwards on the National Priorities List
- **October 1990**: EPA, California and the Air Force entered a CERCLA Federal Facility Agreement (FFA).
- **2007**: Air Force and EPA issued a ROD for the South AFRL. This ROD, among other things, established a VICB to address groundwater contaminated with PCE. The PCE toxicity value used to establish the VICB was the toxicity value established by OEHHA. IRIS had not yet established a toxicity value for PCE.
- **2012**: Air Force conducted a 5-year review. In the 5-year review, the Air Force identified several issues that may affect the protectiveness of the remedy, including a new MCL for perchlorate and new IRIS values for PCE and TCE.
- **January 2014**: Air Force submitted a draft ESD for the South AFRL. The draft ESD proposed to add a newly promulgated California MCL for perchlorate, apply the updated IRIS value for TCE, and change the PCE value to apply the 2012 EPA IRIS value for PCE, which is 23 times less stringent than the OEHHA value. California and EPA objected to the proposed modification to the PCE toxicity value.
- **May 2014**: Air Force issued a Draft Final ESD containing the EPA IRIS value for PCE.
- **June 9, 2014**: California initiated informal dispute over four issues arising from the Draft Final ESD. Three of those issues were resolved in informal dispute.
- **August 22, 2014**: California initiated formal dispute over the toxicity value to be applied for the PCE VICB.
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Appointment

From: Adm15Wheeler.Calendar [Adm15Wheeler.Calendar@epa.gov]
Sent: 10/31/2018 6:20:28 PM
To: Adm15Wheeler.Calendar [Adm15Wheeler.Calendar@epa.gov]; Bodine, Susan [bodine.susan@epa.gov]; Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Azad, Ava [Azad.Ava@epa.gov]; Wright, Peter [wright.peter@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Cook, Steven [cook.steven@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]; Woolford, James [Woolford.James@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Fotouhi, David [fotouhi.david@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Herrera, Angeles [Herrera.Angeles@epa.gov]; Maldonado, Lewis [Maldonado.Lewis@epa.gov]; Rodgers, Ryan [Rodgers.Ryan@epa.gov]; Loving, Shanita [Loving.Shanita@epa.gov]; Stalcup, Dana [Stalcup.Dana@epa.gov]; Dunlap, David [dunlap.david@epa.gov]; Jackson, Ryan [jackson.ryan@epa.gov]; Stoker, Michael B. [stoker.michael@epa.gov]
CC: Ball, Harold [Ball.Harold@epa.gov]; Dirscherl, Christopher [dirscherl.christopher@epa.gov]; Minor, Dustin [Minor.Dustin@epa.gov]

Subject: Briefing: Edwards Air Force Base dispute/CERCLA dispute
Attachments: Final Agenda Edwards Dispute Admin Briefing 11-2-18.docx; Final one pager _ Edwards Dispute Admin Briefing November 2 2018.docx; Final Edwards AFB FFA Dispute Briefing Paper for Acting Administrator Wheeler November 2018 .docx
Location: Alm Room/ Region 9 will join by Video Conference

Start: 11/6/2018 6:15:00 PM
End: 11/6/2018 7:15:00 PM
Show Time As: Busy

Edwards Air Force Base – South Air Force Research Laboratory (AFRL), CA
CERCLA Federal Facility Agreement Formal Dispute Resolution
Briefing for Acting Administrator Wheeler
November 6, 2018

Purpose

Present options and associated policy implications for consideration to resolve the Edwards Air Force Base South AFRL CERCLA § 120 Federal Facility Agreement (FFA) dispute. The Air Force elevated this dispute to the EPA Administrator for resolution on January 31, 2018 in accordance with the FFA's dispute resolution process.

Posture of the Dispute

The parties agree the primary issue at dispute is whether to update a 2007 Record of Decision (ROD) to apply the 2012 EPA Integrated Risk Information System (IRIS) toxicity value for tetrachloroethene (PCE) to determine the appropriate vapor intrusion compliance boundary (VICB) calculation and the indoor air monitoring and compliance levels at South AFRL. The 2007 ROD selected the VICB and monitoring and compliance levels for PCE using a 1991 California Office of Environmental Health Hazard Assessment (OEHHA) toxicity value, as no IRIS value existed at the time of ROD signature. EPA established an IRIS value for PCE, which is less stringent than the 1991 OEHHA value, in 2012. OEHHA updated its PCE toxicity value in 2016 to a value slightly more stringent than its 1991 OEHHA value.

The Air Force would like to modify the ROD to apply the 2012 IRIS PCE toxicity value.

The California Department of Toxic Substances Control (DTSC) and Lahontan Regional Water Quality Control Board (Water Board) (together "California") would like to either retain the 1991 OEHHA value included in the ROD or apply the 2016 updated OEHHA value.

The dispute raises policy and precedent considerations. Resolution of the dispute will likely be a balancing of the countervailing policy considerations, described below, as they relate to the various options for resolution.

Background of the Dispute

Edwards Air Force Base (Edwards) is an active Air Force base on the National Priorities List (NPL). EPA, the Air Force, DTSC, and the Water Board are signatories to a 1990 CERCLA § 120 FFA for Edwards. The FFA establishes a framework for the investigation and cleanup, including a process for dispute resolution, beginning with informal dispute and ending with the EPA Administrator.

The FFA has the following process for dispute resolution: informal dispute, elevation to formal dispute for resolution by the Dispute Resolution Committee (Superfund Division Director-level), elevation to the Senior Executive Committee (Regional Administrator-level), and, finally, elevation to the EPA Administrator.

In 2007, the Air Force and EPA, with the concurrence of California, issued a ROD for South AFRL using, among other things, the OEHHA toxicity value for PCE. In 2014, the Air Force submitted a draft Explanation of Significant Differences (ESD) in response to issues identified in a 2012 five-year review.

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Specifically, the draft ESD proposed to update the Maximum Contaminant Level in groundwater for perchlorate to address a future protectiveness concern. The ESD also proposed to update the inhalation toxicity values for PCE and trichloroethylene (TCE).

In June 2014, California invoked informal dispute in response to the Air Force's proposal in the draft final ESD to modify the PCE toxicity value to apply the 2012 IRIS PCE toxicity value. The Region 9 Regional Administrator (RA) issued a decision in June 2015 stating that the change from the OEHHA value to the IRIS value would require a ROD amendment. The Air Force elevated the dispute to the Administrator in July 2015. In January 2016, at the request of the Office of the Administrator, the dispute was deferred for 15 months to allow California to update its PCE toxicity value,[1] and the dispute was referred to the Senior Executive Committee (RA level). On January 17, 2018, the Acting RA issued a decision stating that the PCE toxicity value in the 2007 ROD would not be modified as it remained protective, no site-specific factors supported modifying the value, and upholding cleanup levels selected in RODs provides certainty to the public, potentially responsible parties (PRPs), and parties interested in making use of CERCLA sites for redevelopment or reuse.

On January 31, 2018, the Air Force elevated the dispute to the Administrator requesting that the Administrator direct the Air Force to adopt EPA's 2012 PCE toxicity value at SAFRL.[2]

In the meantime, DTSC published a proposed Toxicity Criteria Rule[3] that establishes a process for selection of toxicity values, including a value for PCE. The public comment period for the rule closed, and DTSC submitted a final version of the rule to the Office of Administrative Law for review and publication in late July. DTSC promulgated the final rule on September 4, 2018, effective immediately. California intends to formally propose that EPA identify the rule to be an applicable or relevant and appropriate requirement (ARAR) at Superfund sites in California.

This issue is also the subject of a formal dispute at another operable unit (OU) at Edwards, and may arise again at other OUs at Edwards or at other Superfund sites in California.

Policy and Legal Considerations of this Dispute

1. EPA Guidance on Determining Which Toxicity Value to Apply in Superfund Risk Assessment

CERCLA § 121(d) requires that on-site remedial actions attain (or waive) federal or more stringent state ARARs. If a chemical-specific ARAR exists, it must be attained (or waived) upon completion of the remedial action. If no chemical-specific ARAR exists, a risk assessment is conducted to establish a risk-based value to be applied at the site for the chemical in question.

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[1] OEHHA adopted its updated PCE inhalation unit risk value on September 8, 2016.

[2] The Air Force also requested that the Administrator: find that EPA Region 9 did not follow the FFA dispute procedures or the NCP by issuing a decision in response to the Air Force's 2015 elevation of this dispute stating that the Air Force's proposed change to the PCE toxicity value would require a ROD amendment; confirm that EPA must follow all FFA dispute resolution procedures, including time frames, absent all parties' agreement to a change; confirm or clarify EPA's guidance on the hierarchy of toxicity values to be used when multiple toxicity values exist for a given contaminant; and clarify the appropriate process for determining whether a change is "significant" (triggering an ESD) versus "fundamental" (triggering a ROD amendment). See Appendix 1 for further discussion of these additional requests and why EPA does not need to respond to these requests to resolve the dispute.

[3] The Notice of Proposed Rulemaking was issued on August 4, 2017.

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OSWER memorandum "Human Health Toxicity Values in Superfund Risk Assessment" (Hierarchy memorandum) discusses a hierarchy of toxicity values when carrying out a Superfund risk assessment.[4] The guidance provides three different tiers of toxicity values. Tier 1 is EPA's IRIS. Tier 2 is EPA's Provisional Peer Reviewed Toxicity Values, which are not relevant in this dispute. Tier 3 is "Other Toxicity Values." In this case, OEHHA's toxicity value is a Tier 3 value.

The Hierarchy memorandum indicates that IRIS is generally the preferred source of human health toxicity values. The memorandum states, "This revised hierarchy recognizes that EPA should use the best science available on which to base risk assessments. In general, if health assessment information is available in the Integrated Risk Information System . . . for the contaminant under evaluation, risk assessors normally need not search further for additional sources of information."

However, the memorandum also recognizes that there may be other sources of toxicological information: "IRIS is not the only source of toxicology information, and in some cases more recent, credible and relevant data may come to the Agency's attention. In particular, toxicological information other than in IRIS may be brought to the Agency by outside parties. Such information should be considered along with the data in IRIS in selecting toxicological values; ultimately, the Agency should evaluate risk based upon its best scientific judgment and consider all credible and relevant information available to it."

The Hierarchy memorandum further states, "EPA and state personnel may use and accept other technically sound approaches, either on their own initiative, or at the suggestion of potentially responsible parties, or other interested parties."

2. Consistency with CERCLA and the National Contingency Plan

Based in part in response to comments that PRPs need certainty in remedy selection, EPA stated in the preamble to the 1990 NCP, "Once a ROD is signed and a remedy chosen, EPA will not reopen that decision unless the new or modified requirement calls into question the protectiveness of the selected remedy. . . If ARARs were not frozen at . . . [the time of ROD signature], promulgation of a new or modified requirement could result in a reconsideration of the remedy and a restart of the lengthy design process, even if protectiveness is not compromised. This lack of certainty could adversely affect the operation of the CERCLA program, would be inconsistent with Congress' mandate to expeditiously cleanup sites and could adversely affect PRP negotiations, as noted by commenters." (55 Fed. Reg. at p. 8757, March 8, 1990).

The preamble states that, to address this matter of certainty in remedy selection, the final NCP includes the following provision: § 300.430(f)(1)(ii)(B): "On-site remedial actions selected in a ROD must attain those ARARs that are identified at the time of ROD signature or provide grounds for invoking a waiver under § 300.430(f)(1)(ii)(C)(3). (1) Requirements that are promulgated or modified after ROD signature must be attained (or waived) only when determined to be applicable or relevant and appropriate and necessary to ensure that the remedy is protective of human health and the environment."

In the current dispute, the OEHHA toxicity value(s) and the IRIS toxicity values are not ARARs.

Consistent with CERCLA and the NCP, a ROD is modified when a remedy is not protective; however, nothing in CERCLA or the NCP prohibits a ROD from being modified even if the current remedy is protective so long as the remedy, as modified, remains protective.

[4] OSWER Directives 9285.7-53 (2003), 9285.7-16 (1993), and 9285.7-86 (2013).

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In practice, EPA has modified RODs when the original remedy remained protective. For example, EPA recently proposed to modify a ROD at Portland Harbor, OR, at the request of a PRP. The PRP sought to have EPA apply a more recent, less stringent IRIS value for carcinogenic polycyclic aromatic hydrocarbons even though the cleanup level in the existing ROD is still considered protective. As with the Air Force position at Edwards, the Portland Harbor PRP sought to have EPA modify a protective remedy to apply a less stringent value. There are several key distinctions between Edwards and Portland Harbor:

- At Portland Harbor, the updated IRIS value was released three weeks after ROD signature where, at Edwards, the PCE IRIS value was released five years after ROD signature;
- At Portland Harbor, the comparison is between an older IRIS value and an updated IRIS value rather than a state value and an IRIS value as in the Edwards dispute;
- At Portland Harbor, the Oregon Department of Environmental Quality did not oppose the proposal to modify the ROD to apply the updated, less stringent IRIS value where, at Edwards, California is a party to the FFA and strongly opposes adopting IRIS; and
- Modification of the ROD to apply the updated IRIS value at Portland Harbor will result in an approximately $35 million cost savings in implementing the remedy while, at Edwards, the Air Force has stated that there is minimal cost difference at the affected Operable Units between applying the 1991 OEHHA value, the 2016 OEHHA value, and the IRIS value.

3. Comparison of the OEHHA and IRIS Approaches to Setting PCE Toxicity Values

The IRIS and OEHHA PCE values use the same underlying data and models. Both went through an extensive public comment period, received independent scientific peer review, and reflect reasoned scientific judgments. Both EPA and OEHHA developed values to protect the full population, including sensitive subpopulations.

In developing the IRIS value, EPA's National Center for Environmental Assessment (NCEA) concluded certain estimates of metabolism were too uncertain to be used with confidence. California OEHHA also recognized large uncertainties in those estimates, but chose a different way to reflect those estimates.

California OEHHA also chose to utilize estimates of human risk from a type of rat cancer that the IRIS assessment did not use (following the majority advice of the National Academy of Sciences (NAS) peer review panel). There was a minority group of scientists on the NAS panel who felt the rat cancers (a kind of leukemia) should be used in estimating human cancer risk. The IRIS assessment summary notes that higher cancer risks would result if one used that cancer type and that there were differing scientific views on that issue.

Finally, OEHHA took a different approach than did the IRIS assessment, by averaging the risk estimates from different types of laboratory animal cancers rather than the IRIS approach of using only the cancers in which it had the most confidence. The OEHHA approach resulted in an action level that is an order of magnitude lower (more stringent) than the level called for using the IRIS approach.

Although OEHHA's and EPA's review of the data resulted in different conclusions, both are reasoned scientific judgments reached on a complex dataset.

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4. Implications for the Superfund Program

Depending on the resolution, the outcome of this dispute could have national implications for the Superfund program.

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

5. Implications for State Relations & Potential for Litigation

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

6. Cost Considerations

The NCP includes cost as a potential consideration to evaluate when considering whether a ROD modification is appropriate. As a policy matter, cost may be a reasonable factor to consider where a request is made to reopen or change a protective, selected remedy.

In this case, Air Force has stated that the cost difference for the South AFRL vapor intrusion remedy is minimal between application of the 1991 OEHHA value, the 2016 OEHHA value, and the 2012 IRIS value. The Air Force has stated that if it needed to construct additional buildings at Edwards within the South AFRL VICB, for which there are no current plans, the estimate for installing a passive vapor intrusion mitigation system per building is approximately $100,000.

Because the cost difference is minimal, this consideration is not included under each of the options below.

Dispute Resolution Options Under Consideration

Option 1. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Option 2. Ex. 5 Deliberative Process (DP)

Option 3. Ex. 5 Deliberative Process (DP)

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Options for Resolution

Option 1. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

California Position

Ex. 5 Deliberative Process (DP)

Air Force Position

Ex. 5 Deliberative Process (DP)

Key Policy/Legal Implications

Ex. 5 Deliberative Process (DP)

Option 2. Ex. 5 Deliberative Process (DP)

California Position

Ex. 5 Deliberative Process (DP)

Air Force Position

Ex. 5 Deliberative Process (DP)

Key Policy/Legal Implications

Ex. 5 Deliberative Process (DP)

Option 3. Ex. 5 Deliberative Process (DP)

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Ex. 5 Deliberative Process (DP)

Air Force Position

Ex. 5 Deliberative Process (DP)

Key Policy/Legal Implications

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Appendix 1: Air Force's requests from January 31, 2018 dispute elevation letter

In its January 31, 2018 dispute elevation letter, the Air Force requested that the Administrator:

1) direct the Air Force to adopt EPA's 2012 PCE toxicity value at SAFRL;
2) find that EPA Region 9 did not follow the FFA dispute procedures or the NCP by issuing a decision in response to the Air Force's 2015 elevation of this dispute stating that the Air Force's proposed change to the PCE toxicity value would require a ROD amendment;
3) confirm that EPA must follow all FFA dispute resolution procedures, including time frames, absent all parties' agreement to a change;
4) confirm or clarify EPA's guidance on the hierarchy of toxicity values to be used when multiple toxicity values exist for a given contaminant; and
5) clarify the appropriate process for determining whether a change is "significant" (triggering an ESD) versus "fundamental" (triggering a ROD amendment).

Ex. 5 Deliberative Process (DP)

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Appendix 2: Comparison of OEHHA versus IRIS outputs in the CERCLA risk range

The 2007 ROD set a Remedial Action Objective (RAO) of 10^{-6} as the appropriate cancer risk target for establishing cleanup levels and VICB for PCE.

At a 10^{-6} cancer risk target, applying the OEHHA toxicity value translates into a 2 µg/m3 concentration of PCE in indoor air, while applying the IRIS toxicity value translates into a 47 µg/m3 concentration of PCE in indoor air.

The boundaries of the geographic area identified in the 2007 ROD for vapor intrusion were based on the OEHHA toxicity value; those same boundaries would be deemed to correspond to a cancer risk target of $4.2x\ 10^{-8}$, if evaluated using the 2012 IRIS toxicity value. Likewise, the smaller geographic area proposed by the Air Force for vapor intrusion (also identified using 10^{-6} as the appropriate cancer risk target, but instead using the IRIS toxicity value) would be deemed to correspond to a cancer risk target of $2.3x\ 10^{-5}$, if evaluated using the OEHHA toxicity value.

OEHHA	
Inhalation Cancer Unit Risk (IUR) = $6.1x10^{-6}$ [1/(µg/m3)]	
Concentration in Indoor Air (µg/m3)	**Risk**
47	$2.3x10^{-5}$
2	$1x10^{-6}$

IRIS	
Inhalation Cancer Unit Risk (IUR) = $2.6x10^{-7}$ [1/(µg/m3)]	
Concentration in Indoor Air (µg/m3)	**Risk**
47	$1x10^{-6}$
2	$4.2x10^{-8}$

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Appendix 3: Chronology of the Dispute

- **August 30, 1990**: EPA listed Edwards on the National Priorities List
- **October 1990**: EPA, California and the Air Force entered a CERCLA Federal Facility Agreement (FFA).
- **2007**: Air Force and EPA issued a ROD for the South AFRL. This ROD, among other things, established a VICB to address groundwater contaminated with PCE. The PCE toxicity value used to establish the VICB was the toxicity value established by OEHHA. IRIS had not yet established a toxicity value for PCE.
- **2012**: Air Force conducted a 5-year review. In the 5-year review, the Air Force identified several issues that may affect the protectiveness of the remedy, including a new MCL for perchlorate and new IRIS values for PCE and TCE.
- **January 2014**: Air Force submitted a draft ESD for the South AFRL. The draft ESD proposed to add a newly promulgated California MCL for perchlorate, apply the updated IRIS value for TCE, and change the PCE value to apply the 2012 EPA IRIS value for PCE, which is 23 times less stringent than the OEHHA value. California and EPA objected to the proposed modification to the PCE toxicity value.
- **May 2014**: Air Force issued a Draft Final ESD containing the EPA IRIS value for PCE.
- **June 9, 2014**: California initiated informal dispute over four issues arising from the Draft Final ESD. Three of those issues were resolved in informal dispute.
- **August 22, 2014**: California initiated formal dispute over the toxicity value to be applied for the PCE VICB.
- **November 2014 & January 2015**: The Dispute Resolution Committee (DRC) convened by video teleconference to attempt to resolve the dispute. EPA took the position that a change in the PCE toxicity value constituted a fundamental change and required a ROD amendment. California supported this position. Air Force did not agree, and proposed to do an ESD with public comment. The DRC was unable to resolve the dispute and elevated the dispute to the Senior Executive Committee (SEC).
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- **March 30, 2018**: OECA AA, OLEM Acting AA, and Region 9 Acting RA (via VTC) met with representatives from the Air Force and California to discuss the parties' positions on the dispute.
- **September 4, 2018**: California promulgated its Toxicity Criteria Rule.

ED_005043G_00087714-00014

Appointment

From: Bodine, Susan [bodine.susan@epa.gov]
Sent: 11/1/2018 9:40:34 PM
To: Bodine, Susan [bodine.susan@epa.gov]; Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Azad, Ava [Azad.Ava@epa.gov]; Stoker, Michael B. [stoker.michael@epa.gov]
CC: Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Maldonado, Lewis [Maldonado.Lewis@epa.gov]; Dirscherl, Christopher [Dirscherl.Christopher@epa.gov]; Herrera, Angeles [Herrera.Angeles@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Openchowski, Charles [openchowski.charles@epa.gov]; Miles, Erin [Miles.Erin@epa.gov]; Johnson, SusanA [Johnson.SusanA@epa.gov]; Stalcup, Dana [Stalcup.Dana@epa.gov]; Fotouhi, David [fotouhi.david@epa.gov]; Anderson, RobinM [Anderson.RobinM@epa.gov]; Ammon, Doug [Ammon.Doug@epa.gov]; Fairbanks, Brianna [Fairbanks.Brianna@epa.gov]; Kelley, Meghan [kelley.meghan@epa.gov]; Young, Dianna [Young.Dianna@epa.gov]; Ball, Harold [Ball.Harold@epa.gov]; Minor, Dustin [Minor.Dustin@epa.gov]; Bailey, Ethel [Bailey.Ethel@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Burchette, John [Burchette.John@epa.gov]; Woolford, James [Woolford.James@epa.gov]

Subject: Prep for Administrator's meeting on Edwards Air Force Base Dispute/CERCLA w/R9/OLEM
Attachments: Final Agenda Edwards Dispute Admin Briefing 11-2-18.docx; Final one pager _ Edwards Dispute Admin Briefing November 2 2018.docx; Final Edwards AFB FFA Dispute Briefing Paper for Acting Administrator Wheeler November 2018 .docx
Location: 3204 WJC-South, conference number Ex. 6 Personal Privacy (PP)

Start: 11/5/2018 9:30:00 PM
End: 11/5/2018 10:00:00 PM
Show Time As: Busy

Message

From: Bodine, Susan [bodine.susan@epa.gov]
Sent: 5/10/2019 9:18:43 PM
To: Stoker, Michael B. [stoker.michael@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Wright, Peter [wright.peter@epa.gov]; Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Dunlap, David [dunlap.david@epa.gov]
CC: Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Traylor, Patrick [traylor.patrick@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Shiffman, Cari [Shiffman.Cari@epa.gov]; Branning, Hannah [Branning.Hannah@epa.gov]
Subject: Edwards AFB
Attachments: Edwards Dispute Decision - Final Draft (5-10-2019).docx

All,

The attached final draft reflects the Administrator's decision regarding the Air Force Dispute regarding the South AFRL operable unit at Edwards AFB. We plan to forward this to the Administrator's office for signature on Monday.

Thanks to all for your help in bringing this matter to conclusion.

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

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Message

From: Michaud, John [Michaud.John@epa.gov]
Sent: 5/9/2019 4:13:31 PM
To: Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]
Subject: FW: Edwards
Attachments: Edwards Dispute Resolution Discussion Draft -- 5-9-19 - final version for discussion at 5-9 AA meeting.docx

Flag: Follow up

Matt & David -- In advance of this afternoon's AA-level meeting to prepare for tomorrow's Administrator meeting on the Edwards AFB Federal Facility dispute, attached is the latest version of the Administrator's decision.

The decision affirms the Region IX decision on this dispute. Meaning, the Administrator decided to retain the PCE toxicity value in the 2007 ROD for the South AFRL site. The Administrator is also withdrawing the June 9, 2015 decision of the Region IX RA.

Ex. 5 AC/DP

Please let me know if you would like to meet prior to the 4:30 meeting today. Also, I'm happy to cover this meeting on OGC's behalf.

Thanks.

John

John R Michaud

Associate General Counsel
Solid Waste and Emergency Response Law Office
202-564-5518
michaud.john@epa.gov

From: Azad, Ava
Sent: Thursday, May 09, 2019 10:55 AM
To: Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Woolford, James <Woolford.James@epa.gov>; Johnson, SusanA <Johnson.SusanA@epa.gov>; Fitz-James, Schatzi <Fitz-James.Schatzi@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Anderson, RobinM <Anderson.RobinM@epa.gov>; Kelley, Meghan <kelley.meghan@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Maldonado, Lewis <Maldonado.Lewis@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Michaud, John <Michaud.John@epa.gov>; Lyons, John <Lyons.John@epa.gov>; Burchette, John <Burchette.John@epa.gov>; Lewis, Jen <Lewis.Jen@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Miles, Erin <Miles.Erin@epa.gov>; Minor, Dustin <Minor.Dustin@epa.gov>; Maddox, Doug <Maddox.Doug@epa.gov>; Ammon, Doug <Ammon.Doug@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>; Seter, David <Seter.David@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Stalcup, Dana <Stalcup.Dana@epa.gov>; Openchowski, Charles <openchowski.charles@epa.gov>; Lowery, Brigid <Lowery.Brigid@epa.gov>; Fairbanks, Brianna <Fairbanks.Brianna@epa.gov>; Herrera, Angeles <Herrera.Angeles@epa.gov>; Gartner, Lois <Gartner.Lois@epa.gov>;

Schutz, Michelle <Schutz.Michelle@epa.gov>
Subject: FW: Edwards

Good morning,

Thank you for your responses regarding the final edits/comments on the proposed Edwards decision.

Please see message below and attached document that we sent to Susan and Larry in preparation for the AA-level meeting this afternoon. No other updates to report at this time.

Thanks,
Ava

Ava Azad
Attorney-Advisor
Federal Facilities Enforcement Office, 2209B
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
Washington, D.C. 20460
P: (202) 564-4473
F: (202) 501-0069

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From: Azad, Ava
Sent: Thursday, May 09, 2019 9:25 AM
To: Starfield, Lawrence <Starfield.Lawrence@epa.gov>; Bodine, Susan <bodine.susan@epa.gov>
Cc: Leff, Karin <Leff.Karin@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Dalzell, Sally <Dalzell.Sally@epa.gov>
Subject: RE: Edwards

Larry and Susan,

Attached is an updated version of the Edwards Administrator decision with the last remaining comments/edits. For ease of review, I accepted all of the Track Changes from the previous version we received from Susan (5/2/19), except in places where suggested edits were made to that language.

Several of the edits are stylistic/language edits.

The last two remaining substantive comments from other offices are:

Ex. 5 - AC/DP

Aside from the above two comments, the other offices have said that they support the proposed decision.

Please note that Dave Bussard said that Jennifer Orme-Zavaleta has a conflict with the Friday meeting with the Administrator. Unless we feel otherwise, ORD is comfortable not being represented at that meeting.

Thank you,
Ava

Ava Azad
Attorney-Advisor
Federal Facilities Enforcement Office, 2209B
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
Washington, D.C. 20460
P: (202) 564-4473
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Message

From: Lewis, Jen [Lewis.Jen@epa.gov]
Sent: 5/6/2019 1:55:26 PM
To: Fotouhi, David [Fotouhi.David@epa.gov]
CC: Michaud, John [Michaud.John@epa.gov]; Miles, Erin [Miles.Erin@epa.gov]
Subject: FW: Edwards - Latest (5/2/19) Draft of Administrator Decision & Upcoming Meetings
Attachments: Table of Comments on Edwards Admin Decision v.4.29.19 response.docx; Edwards Dispute Resolution Discussion 5-2-19 redline of 4-29-19.docx; Edwards Dispute Resolution Discussion Draft 5-2-19 redline of 4-30 - FFEO.docx

David – the latest draft is attached.

Jen Lewis
Deputy Associate General Counsel
Solid Waste and Emergency Response Law Office
(202) 564-2097

From: Azad, Ava
Sent: Friday, May 03, 2019 10:58 AM
To: Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Herrera, Angeles <Herrera.Angeles@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Seter, David <Seter.David@epa.gov>; Maldonado, Lewis <Maldonado.Lewis@epa.gov>; Fairbanks, Brianna <Fairbanks.Brianna@epa.gov>; Minor, Dustin <Minor.Dustin@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Burchette, John <Burchette.John@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Woolford, James <Woolford.James@epa.gov>; Stalcup, Dana <Stalcup.Dana@epa.gov>; Anderson, RobinM <Anderson.RobinM@epa.gov>; Johnson, SusanA <Johnson.SusanA@epa.gov>; Openchowski, Charles <openchowski.charles@epa.gov>; Michaud, John <Michaud.John@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lowery, Brigid <Lowery.Brigid@epa.gov>; Fitz-James, Schatzi <Fitz-James.Schatzi@epa.gov>; Ammon, Doug <Ammon.Doug@epa.gov>; Miles, Erin <Miles.Erin@epa.gov>; Lyons, John <Lyons.John@epa.gov>; Lewis, Jen <Lewis.Jen@epa.gov>; Maddox, Doug <Maddox.Doug@epa.gov>; Kelley, Meghan <kelley.meghan@epa.gov>
Subject: Edwards - Latest (5/2/19) Draft of Administrator Decision & Upcoming Meetings

All,

Please see attached the latest version(s) of the Edwards dispute proposed Administrator decision and table of (previous round) of comments, with Susan's responses.

As we understand it, the 4-29-19 version attached is the version Susan and Larry had already revised before we met with them on Tuesday, and includes the edits at that time in Track Changes. The 4-30 version has many of those changes accepted, and includes further edits made as a result of the edits/comments we shared with Susan and Larry. We have added a few edits to the 4-30 version, which we believe to be the latest version off of which we should all be working.

A meeting has been scheduled for the principles to meet **with the Administrator on Friday, May 10 from 11:15am – 12:00pm EST**. The invitees include: Susan Bodine, Larry Starfield, Mike Stoker, Peter Wright, Steven Cook, Matt Leopold, David Fotouhi, and Jennifer Orme-Zavaleta.

Susan would like to have an **AA-level meeting on Wednesday or Thursday** (this would include the team) to prepare for the Friday meeting with the Administrator. Our front office will send a scheduler for this meeting. **Please let your leadership know that they will be receiving this meeting invite from Susan and the purpose for the meeting (i.e., for the AAs to meet and discuss the draft decision before meeting with the Administrator on Friday).**

I will schedule a **meeting for the Team on Tuesday afternoon EST** for us to touch base before the AA and Administrator meetings.

Please **reply all with any comments on the latest draft** of the decision before our Team meeting on Tuesday so that we can discuss any outstanding comments on our call.

Please let me know if you have any questions.

Thank you,
Ava

Ava Azad
Attorney-Advisor
Federal Facilities Enforcement Office, 2209B
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
Washington, D.C. 20460
P: (202) 564-4473
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From: Bodine, Susan
Sent: Thursday, May 02, 2019 6:34 PM
To: Azad, Ava <Azad.Ava@epa.gov>; Starfield, Lawrence <Starfield.Lawrence@epa.gov>
Cc: Leff, Karin <Leff.Karin@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Dalzell, Sally <Dalzell.Sally@epa.gov>
Subject: RE: Edwards Decision - Consolidated Comments on 4.29.19 Version

Revision, red-lined to two prior versions. Also response to the TOC.

There was another version created prior to receiving your edits hence the two redlines to make it easier to figure out what changed. Feel free to share with the team.

Susan

From: Azad, Ava
Sent: Tuesday, April 30, 2019 3:57 PM
To: Bodine, Susan <bodine.susan@epa.gov>; Starfield, Lawrence <Starfield.Lawrence@epa.gov>
Cc: Leff, Karin <Leff.Karin@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Dalzell, Sally <Dalzell.Sally@epa.gov>
Subject: Edwards Decision - Consolidated Comments on 4.29.19 Version

Susan, Larry,

Please see attached the draft Edwards decision, with consolidated comments from all offices and the Region on the latest version we received from Susan over the weekend. I am also attaching a table with the main comments from the group. These are the same as indicated in the paper, but I thought pulling out the key comments might help in our discussion.

Thank you,
Ava

Ava Azad
Attorney-Advisor
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U.S. Environmental Protection Agency
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Message

From: Lewis, Jen [Lewis.Jen@epa.gov]
Sent: 5/3/2019 8:43:46 PM
To: Fotouhi, David [Fotouhi.David@epa.gov]
CC: Michaud, John [Michaud.John@epa.gov]; Miles, Erin [Miles.Erin@epa.gov]; Johnson, SusanA [Johnson.SusanA@epa.gov]
Subject: Edwards - meetings next week
Attachments: Table of Comments on Edwards Admin Decision v.4.29.19 response.docx; Edwards Dispute Resolution Discussion 5-2-19 redline of 4-29-19.docx; Edwards Dispute Resolution Discussion Draft 5-2-19 redline of 4-30 - FFEO.docx

David – an Administrator meeting is scheduled for next Friday, May 10, on the Edwards AFB dispute. Susan Bodine is setting up an AA-level meeting in advance of that meeting (please see Ava's email below for a full explanation). We will review the current draft of the decision, and be ready to discuss at reg review on Tuesday. If you think we need to set up a separate briefing for Matt, let me know.

Jen

Jen Lewis
Deputy Associate General Counsel
Solid Waste and Emergency Response Law Office
(202) 564-2097

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Sent: Friday, May 03, 2019 10:58 AM
To: Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Herrera, Angeles <Herrera.Angeles@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Seter, David <Seter.David@epa.gov>; Maldonado, Lewis <Maldonado.Lewis@epa.gov>; Fairbanks, Brianna <Fairbanks.Brianna@epa.gov>; Minor, Dustin <Minor.Dustin@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Burchette, John <Burchette.John@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Woolford, James <Woolford.James@epa.gov>; Stalcup, Dana <Stalcup.Dana@epa.gov>; Anderson, RobinM <Anderson.RobinM@epa.gov>; Johnson, SusanA <Johnson.SusanA@epa.gov>; Openchowski, Charles <openchowski.charles@epa.gov>; Michaud, John <Michaud.John@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lowery, Brigid <Lowery.Brigid@epa.gov>; Fitz-James, Schatzi <Fitz-James.Schatzi@epa.gov>; Ammon, Doug <Ammon.Doug@epa.gov>; Miles, Erin <Miles.Erin@epa.gov>; Lyons, John <Lyons.John@epa.gov>; Lewis, Jen <Lewis.Jen@epa.gov>; Maddox, Doug <Maddox.Doug@epa.gov>; Kelley, Meghan <kelley.meghan@epa.gov>
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Please **reply all with any comments on the latest draft** of the decision before our Team meeting on Tuesday so that we can discuss any outstanding comments on our call.

Please let me know if you have any questions.

Thank you,
Ava

Ava Azad
Attorney-Advisor
Federal Facilities Enforcement Office, 2209B
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
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P: (202) 564-4473
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Revision, red-lined to two prior versions. Also response to the TOC.

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Susan

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Cc: Leff, Karin <Leff.Karin@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Dalzell, Sally <Dalzell.Sally@epa.gov>
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Susan, Larry,

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Thank you,
Ava

Ava Azad
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Message

From: Bodine, Susan [bodine.susan@epa.gov]
Sent: 4/17/2019 5:01:36 PM
To: Breen, Barry [Breen.Barry@epa.gov]; Cook, Steven [cook.steven@epa.gov]; Wright, Peter [wright.peter@epa.gov]; Woolford, James [Woolford.James@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]; Stoker, Michael B. [stoker.michael@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Dunlap, David [dunlap.david@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Azad, Ava [Azad.Ava@epa.gov]; Starfield, Lawrence [Starfield.Lawrence@epa.gov]
CC: Shiffman, Cari [Shiffman.Cari@epa.gov]; Branning, Hannah [Branning.Hannah@epa.gov]; Traylor, Patrick [traylor.patrick@epa.gov]
Subject: Straw for Edward AFB response - Deliberative
Attachments: Edwards Dispute Resolution Discussion Draft v2.docx

All,

I had a very brief conversation with Administrator Wheeler about his decision regarding the Edwards AFB dispute. He wants to keep the 2007 PCE toxicity value, but also address the process concerns raised by the Air Force with respect to EPA's handling of this dispute (both the ROD amendment issue and the timeliness issue as it relates to this dispute and future disputes).

At his request, I put together a draft of a letter that addresses all three issues. I have discussed this with Peter Wright, but it has not yet been reviewed by our respective staff. Can you please ask your offices to review and provide comments on this draft, explaining that it is a "straw" (to use Barry's oft-used phrase)?

I will also ask Haley to schedule a meeting with the Administrator and our offices to get his final decision so we can wrap this up.

Ex. 5 - DP

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

This message is CONFIDENTIAL, and may contain legally privileged information. If you are not the intended recipient, or believe you received this communication in error, please delete it immediately, do not copy, and notify the sender. Thank you.

Message

From: Bodine, Susan [bodine.susan@epa.gov]
Sent: 2/22/2019 8:46:12 PM
To: Humphreys, Hayly [humphreys.hayly@epa.gov]; Eby, Natasha [eby.natasha@epa.gov]
CC: Wright, Peter [wright.peter@epa.gov]; Cook, Steven [cook.steven@epa.gov]; Dunlap, David [dunlap.david@epa.gov]; Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Molina, Michael [molina.michael@epa.gov]
Subject: Background Materials for Edwards AFB Dispute meeting March 8
Attachments: Final one pager _ Edwards Dispute Admin Briefing November 2 2018.docx; Final Edwards AFB FFA Dispute Briefing Paper for Acting Administrator Wheeler November 2018 .docx

Background for the March 8 meeting with the Air Force, California, Region 9, OLEM, and OECA on the Air Force's dispute regarding Region 9's decision on cleanup levels for PCE at Edwards AFB.

Andrew was briefed on November 6. He asked for a copy of those briefing materials (and not another briefing).

I will forward an Agenda as well when I get it from staff.

Susan

From: Bodine, Susan
Sent: Friday, November 2, 2018 4:50 PM
To: Eby, Natasha <eby.natasha@epa.gov>; Humphreys, Hayly <humphreys.hayly@epa.gov>; Dickerson, Aaron <dickerson.aaron@epa.gov>
Cc: Starfield, Lawrence <Starfield.Lawrence@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Azad, Ava <Azad.Ava@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Cook, Steven <cook.steven@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <fotouhi.david@epa.gov>; Michaud, John <Michaud.John@epa.gov>; Strauss, Alexis <Strauss.Alexis@epa.gov>; Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Herrera, Angeles <Herrera.Angeles@epa.gov>
Subject: Background Materials for Tuesday Briefing on Ft. Edwards Dispute

Attached are background materials for the Tuesday, November 6 briefing for Acting Administrator Wheeler regarding the Ft. Edwards Air Force Base Superfund dispute.

Tuesday's briefing is to prepare Acting Administrator Wheeler for a not yet scheduled meeting with the Air Force and the State of California, to hear their arguments relating to the dispute.

This matter involves OECA, OLEM, OGC, ORD, and Region 9.

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

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Message

From: Bodine, Susan [bodine.susan@epa.gov]
Sent: 11/2/2018 8:50:25 PM
To: Eby, Natasha [eby.natasha@epa.gov]; Humphreys, Hayly [humphreys.hayly@epa.gov]; Dickerson, Aaron [dickerson.aaron@epa.gov]
CC: Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Azad, Ava [Azad.Ava@epa.gov]; Wright, Peter [wright.peter@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Cook, Steven [cook.steven@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]; Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Leopold, Matt (OGC) [Leopold.Matt@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Herrera, Angeles [Herrera.Angeles@epa.gov]
Subject: Background Materials for Tuesday Briefing on Ft. Edwards Dispute
Attachments: Final Agenda Edwards Dispute Admin Briefing 11-2-18.docx; Final one pager _ Edwards Dispute Admin Briefing November 2 2018.docx; Final Edwards AFB FFA Dispute Briefing Paper for Acting Administrator Wheeler November 2018 .docx

Flag: Flag for follow up

Attached are background materials for the Tuesday, November 6 briefing for Acting Administrator Wheeler regarding the Ft. Edwards Air Force Base Superfund dispute.

Tuesday's briefing is to prepare Acting Administrator Wheeler for a not yet scheduled meeting with the Air Force and the State of California, to hear their arguments relating to the dispute.

This matter involves OECA, OLEM, OGC, ORD, and Region 9.

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

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Message

From: Azad, Ava [Azad.Ava@epa.gov]
Sent: 3/1/2018 9:17:21 PM
To: Bodine, Susan [bodine.susan@epa.gov]; Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Leonard, Paul [leonard.paul@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]
CC: Gaudario, Abigail [Gaudario.Abigail@epa.gov]; Woolford, James [Woolford.James@epa.gov]; Burchette, John [Burchette.John@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Muller, Marie [MULLER.MARIE@EPA.GOV]; Anderson, RobinM [Anderson.RobinM@epa.gov]; Openchowski, Charles [openchowski.charles@epa.gov]; Johnson, SusanA [Johnson.SusanA@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Herrera, Angeles [Herrera.Angeles@epa.gov]; Maldonado, Lewis [Maldonado.Lewis@epa.gov]; Ball, Harold [Ball.Harold@epa.gov]; Dirscherl, Christopher [Dirscherl.Christopher@epa.gov]; Minor, Dustin [Minor.Dustin@epa.gov]; Fairbanks, Brianna [Fairbanks.Brianna@epa.gov]; Young, Dianna [Young.Dianna@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Cook, Steven [cook.steven@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Ammon, Doug [Ammon.Doug@epa.gov]; Stalcup, Dana [Stalcup.Dana@epa.gov]
Subject: RE: Proposed Agenda for Edwards Air Force Base Dispute Meeting, Call-in Number: Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)
Attachments: Edwards AFB SAFRL Dispute -- Key Considerations -- 3.1.18.docx

All:

Please find attached an updated "Key Considerations" document. We removed the last sentence in the answer to Issue 2.

Ava

Ava Azad
Attorney-Advisor
Federal Facilities Enforcement Office, 2202H
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
Washington, D.C. 20460
P: (202) 564-4473
F: (202) 501-0069

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From: Azad, Ava
Sent: Thursday, March 01, 2018 3:20 PM
To: Bodine, Susan <bodine.susan@epa.gov>; Starfield, Lawrence <Starfield.Lawrence@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Leonard, Paul <leonard.paul@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>
Cc: Gaudario, Abigail <Gaudario.Abigail@epa.gov>; Woolford, James <Woolford.James@epa.gov>; Burchette, John <Burchette.John@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Muller, Marie <MULLER.MARIE@EPA.GOV>; Anderson, RobinM <Anderson.RobinM@epa.gov>; Openchowski, Charles <openchowski.charles@epa.gov>; Johnson, SusanA <Johnson.SusanA@epa.gov>; Michaud, John <Michaud.John@epa.gov>; Herrera, Angeles <Herrera.Angeles@epa.gov>; Maldonado, Lewis <Maldonado.Lewis@epa.gov>; Ball, Harold <Ball.Harold@epa.gov>; Dirscherl, Christopher

<Dirscherl.Christopher@epa.gov>; Minor, Dustin <Minor.Dustin@epa.gov>; Fairbanks, Brianna <fairbanks.brianna@epa.gov>; Young, Dianna <Young.Dianna@epa.gov>; Fotouhi, David <fotouhi.david@epa.gov>; Cook, Steven <cook.steven@epa.gov>; Strauss, Alexis <Strauss.Alexis@epa.gov>; Ammon, Doug <Ammon.Doug@epa.gov>; Stalcup, Dana <Stalcup.Dana@epa.gov>
Subject: Proposed Agenda for Edwards Air Force Base Dispute Meeting, Call-in Number: Ex. 6 Personal Privacy (PP)
Ex. 6 Personal Privacy (PP)

All,

Below is a proposed agenda for the meeting this afternoon on the Edwards Air Force Base Dispute. This agenda can be adjusted at the beginning of the meeting if management prefers.

1) Brief summary of the dispute
2) Recommendation and options for resolution
3) Key considerations
4) Additional questions/concerns from OECA/OLEM/OGC leadership
5) Next steps

I have also re-attached the briefing materials here for your convenience.

Thank you.

Ava Azad
Attorney-Advisor
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U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
Washington, D.C. 20460
P: (202) 564-4473
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From: Azad, Ava
Sent: Wednesday, February 28, 2018 3:59 PM
To: Bodine, Susan <bodine.susan@epa.gov>; Starfield, Lawrence <Starfield.Lawrence@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Leonard, Paul <leonard.paul@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>
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Subject: Final Materials Attached for the Edwards Airforce Base Dispute Meeting, Call-in Number: Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)

All,

Attached are the final materials in preparation for tomorrow's meeting. These materials were developed by FFEO, FFRRO, OSRTI, OGC, and Region 9. They are:

1) Recommendation & Options;
2) Chronology of the Dispute; and
3) Key Considerations

We look forward to tomorrow's meeting.

Thank you.

Ava Azad
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U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 2261A)
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-----Original Appointment-----
From: Bodine, Susan
Sent: Monday, February 05, 2018 5:01 PM
To: Bodine, Susan; Starfield, Lawrence; Breen, Barry; Dalzell, Sally; Manzanilla, Enrique; Leonard, Paul; Gervais, Gregory
Cc: Gaudario, Abigail; Woolford, James; Burchette, John; Azad, Ava; Leff, Karin; Muller, Marie; Anderson, RobinM; Openchowski, Charles; Johnson, SusanA; Michaud, John; Herrera, Angeles; Maldonado, Lewis; Ball, Harold; Dirscherl, Christopher; Minor, Dustin; Fairbanks, Brianna; Young, Dianna; Fotouhi, David; Cook, Steven; Strauss, Alexis
Subject: Edwards Airforce Base Dispute, Call-in Number: Ex. 6 Personal Privacy (PP)
When: Thursday, March 01, 2018 4:30 PM-5:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 3204 WJC-South

Message

From: Azad, Ava [Azad.Ava@epa.gov]
Sent: 3/1/2018 8:19:20 PM
To: Bodine, Susan [bodine.susan@epa.gov]; Starfield, Lawrence [Starfield.Lawrence@epa.gov]; Breen, Barry [Breen.Barry@epa.gov]; Dalzell, Sally [Dalzell.Sally@epa.gov]; Manzanilla, Enrique [Manzanilla.Enrique@epa.gov]; Leonard, Paul [leonard.paul@epa.gov]; Gervais, Gregory [Gervais.Gregory@epa.gov]
CC: Gaudario, Abigail [Gaudario.Abigail@epa.gov]; Woolford, James [Woolford.James@epa.gov]; Burchette, John [Burchette.John@epa.gov]; Leff, Karin [Leff.Karin@epa.gov]; Muller, Marie [MULLER.MARIE@EPA.GOV]; Anderson, RobinM [Anderson.RobinM@epa.gov]; Openchowski, Charles [openchowski.charles@epa.gov]; Johnson, SusanA [Johnson.SusanA@epa.gov]; Michaud, John [Michaud.John@epa.gov]; Herrera, Angeles [Herrera.Angeles@epa.gov]; Maldonado, Lewis [Maldonado.Lewis@epa.gov]; Ball, Harold [Ball.Harold@epa.gov]; Dirscherl, Christopher [Dirscherl.Christopher@epa.gov]; Minor, Dustin [Minor.Dustin@epa.gov]; Fairbanks, Brianna [Fairbanks.Brianna@epa.gov]; Young, Dianna [Young.Dianna@epa.gov]; Fotouhi, David [Fotouhi.David@epa.gov]; Cook, Steven [cook.steven@epa.gov]; Strauss, Alexis [Strauss.Alexis@epa.gov]; Ammon, Doug [Ammon.Doug@epa.gov]; Stalcup, Dana [Stalcup.Dana@epa.gov]
Subject: Proposed Agenda for Edwards Air Force Base Dispute Meeting, Call-in Number: Ex. 6 Personal Privacy (PP)
Attachments: Edwards AFB SAFRL Dispute -- Recommendation Options -- 2.28.18.docx; Edwards AFB SAFRL Dispute -- Chronology -- 2.28.18.docx; Edwards AFB SAFRL Dispute -- Key Considerations -- 2.28.18.docx

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1) Brief summary of the dispute
2) Recommendation and options for resolution
3) Key considerations
4) Additional questions/concerns from OECA/OLEM/OGC leadership
5) Next steps

I have also re-attached the briefing materials here for your convenience.

Thank you.

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Subject: Final Materials Attached for the Edwards Airforce Base Dispute Meeting, Call-in Number: Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)

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Subject: Edwards Airforce Base Dispute, Call-in Number: Ex. 6 Personal Privacy (PP)

When: Thursday, March 01, 2018 4:30 PM-5:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 3204 WJC-South

Edwards Air Force Base South Air Force Research Laboratory, CA
Chronology of the Dispute

- **August 30, 1990**: EPA listed Edwards on the National Priorities List.
- **2007**: Air Force and EPA issued a ROD for the South AFRL. This ROD, among other things, established a VICB to address groundwater contaminated with PCE. The PCE toxicity value used to establish the VICB was the toxicity value established by OEHHA. IRIS had not yet established a toxicity value for PCE.
- **2012**: Air Force conducted a 5-year review. In the 5-year review, the Air Force identified several issues that may affect the protectiveness of the remedy, including a new MCL for perchlorate and new IRIS values for PCE and TCE.
- **January 2014**: Air Force submitted a draft ESD for the South AFRL. The draft ESD proposed to add a newly promulgated California MCL for perchlorate, apply the updated IRIS value for TCE, and change the PCE value to apply the 2012 EPA IRIS value for PCE, which is 23 times less stringent than the OEHHA value. California and EPA objected to the proposed modification to the PCE toxicity value.
- **May 2014**: Air Force issued a Draft Final ESD containing the EPA IRIS value for PCE.
- **June 9, 2014**: California initiated informal dispute over four issues arising from the Draft Final ESD. Three of those issues were resolved in informal dispute.
- **August 22, 2014**: California initiated formal dispute over the toxicity value to be applied for the PCE VICB.
- **November 2014 & January 2015**: The Dispute Resolution Committee (DRC) convened by video teleconference to attempt to resolve the dispute. EPA took the position that a change in the PCE toxicity value constituted a fundamental change and required a ROD amendment. California supported this position. Air Force did not agree, and proposed to do an ESD with public comment. The DRC was unable to resolve the dispute and elevated the dispute to the Senior Executive Committee (SEC).
- **May 20, 2015**: The SEC convened by video teleconference, and was unable to resolve the dispute.
- **June 5, 2015**: EPA Region 9 Regional Administrator issued a decision on the dispute, stating that the proposed change to the PCE toxicity value required a ROD amendment.
- **July 8, 2015**: Air Force elevated the dispute to the EPA Administrator.
- **January 27, 2016**: At the request of the Office of the Administrator, the dispute was deferred for 15 months to allow California time to update its PCE toxicity value and the dispute was referred back to the SEC.
- **September 2016**: OEHHA reissued its PCE toxicity value, which was slightly more stringent than the value in the 2007 ROD (which translates to a commercial/industrial screening level of 2.0 μg/m3 versus 2.1 μg/m3).
- **November 2016**: California's Department of Toxic Substances Control (DTSC) issued an advanced notice of proposed rulemaking, the requirements of which include use of OEHHA's 2016 PCE toxicity value.
- **August 4, 2017**: California published its proposed rulemaking. California asserts that the final rule will constitute an Applicable or Relevant and Appropriate Requirement (ARAR) under CERCLA. Air Force disagrees that the rule, as proposed, would constitute an ARAR. EPA will not determine whether the rule is or is not an ARAR until the rule is final.

ED_005043G_00088723-00001

- **August 8, 2017**: The SEC convened to discuss the dispute, and agreed to delay decision on the dispute for 60 days.
- **September 12 & 13, 2017**: Air Force, EPA, and California staff met to discuss the science underlying the 2016 OEHHA PCE value and the framework of the proposed regulation.
- **December 14, 2017**: The SEC reconvened to attempt to reach a resolution on the dispute. However, the parties did not reach consensus.
- **January 17, 2018**: EPA Region 9 Acting Regional Administrator issued a decision on the dispute, finding that there are no compelling or site-specific reasons related to the remedy's protectiveness, efficacy, or cost effectiveness that support modifying the PCE toxicity value in the 2007 ROD. The Acting RA held that the PCE value in the 2007 ROD remains protective, and that the ESD should not address the PCE toxicity value.
- **January 31, 2018**: Air Force elevated the dispute to the EPA Administrator in response to the RA's decision. Air Force's primary request in its elevation letter is that the Administrator direct the Air Force to apply the EPA IRIS value for PCE. Air Force makes additional requests of the Administrator on issues that are not currently or are no longer in dispute. These include: to confirm or clarify the hierarchy of toxicity values to be applied nationally, and to clarify the process for determining when a change is "significant" (triggering an ESD) versus "fundamental" (triggering a ROD amendment).

ED_005043G_00088723-00002

Message

From: Fotouhi, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FEBAF0D56AAB43F8A9174B18218C1182-FOTOUHI, DA]
Sent: 5/10/2019 9:24:28 PM
To: Michaud, John [Michaud.John@epa.gov]
Subject: FW: Edwards AFB
Attachments: Edwards Dispute Decision - Final Draft (5-10-2019).docx

David Fotouhi

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

From: Bodine, Susan
Sent: Friday, May 10, 2019 5:19 PM
To: Stoker, Michael B. <stoker.michael@epa.gov>; Breen, Barry <Breen.Barry@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Dunlap, David <dunlap.david@epa.gov>
Cc: Starfield, Lawrence <Starfield.Lawrence@epa.gov>; Traylor, Patrick <traylor.patrick@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Shiffman, Cari <Shiffman.Cari@epa.gov>; Branning, Hannah <Branning.Hannah@epa.gov>
Subject: Edwards AFB

All,

The attached final draft reflects the Administrator's decision regarding the Air Force Dispute regarding the South AFRL operable unit at Edwards AFB. We plan to forward this to the Administrator's office for signature on Monday.

Thanks to all for your help in bringing this matter to conclusion.

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

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Message

From: Fotouhi, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FEBAF0D56AAB43F8A9174B18218C1182-FOTOUHI, DA]
Sent: 4/17/2019 5:37:26 PM
To: Lewis, Jen (Lewis.Jen@epa.gov) [Lewis.Jen@epa.gov]; Erin Miles [Miles.Erin@epa.gov]
Subject: FW: Straw for Edward AFB response - Deliberative
Attachments: Edwards Dispute Resolution Discussion Draft v2.docx

Forwarding since John is out

David Fotouhi

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

From: Bodine, Susan
Sent: Wednesday, April 17, 2019 1:02 PM
To: Breen, Barry <Breen.Barry@epa.gov>; Cook, Steven <cook.steven@epa.gov>; Wright, Peter <wright.peter@epa.gov>; Woolford, James <Woolford.James@epa.gov>; Gervais, Gregory <Gervais.Gregory@epa.gov>; Stoker, Michael B. <stoker.michael@epa.gov>; Strauss, Alexis <Strauss.Alexis@epa.gov>; Manzanilla, Enrique <Manzanilla.Enrique@epa.gov>; Leopold, Matt (OGC) <Leopold.Matt@epa.gov>; Fotouhi, David <Fotouhi.David@epa.gov>; Michaud, John <Michaud.John@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Dunlap, David <dunlap.david@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Leff, Karin <Leff.Karin@epa.gov>; Dalzell, Sally <Dalzell.Sally@epa.gov>; Azad, Ava <Azad.Ava@epa.gov>; Starfield, Lawrence <Starfield.Lawrence@epa.gov>
Cc: Shiffman, Cari <Shiffman.Cari@epa.gov>; Branning, Hannah <Branning.Hannah@epa.gov>; Traylor, Patrick <traylor.patrick@epa.gov>
Subject: Straw for Edward AFB response - Deliberative

All,

I had a very brief conversation with Administrator Wheeler about his decision regarding the Edwards AFB dispute. He wants to keep the 2007 PCE toxicity value, but also address the process concerns raised by the Air Force with respect to EPA's handling of this dispute (both the ROD amendment issue and the timeliness issue as it relates to this dispute and future disputes).

At his request, I put together a draft of a letter that addresses all three issues. I have discussed this with Peter Wright, but it has not yet been reviewed by our respective staff. Can you please ask your offices to review and provide comments on this draft, explaining that it is a "straw" (to use Barry's oft-used phrase)?

I will also ask Haley to schedule a meeting with the Administrator and our offices to get his final decision so we can wrap this up.

Ex. 5 - DP

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

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Sent: 11/3/2018 7:21:48 PM
To: Maher, Lauren [Maher.Lauren@epa.gov]; Veney, Carla [Veney.Carla@epa.gov]
Subject: Fwd: Background Materials for Tuesday Briefing on Ft. Edwards Dispute
Attachments: Final Agenda Edwards Dispute Admin Briefing 11-2-18.docx; ATT00001.htm; Final one pager _ Edwards Dispute Admin Briefing November 2 2018.docx; ATT00002.htm; Final Edwards AFB FFA Dispute Briefing Paper for Acting Administrator Wheeler November 2018 .docx; ATT00003.htm

For Matt's Monday night folder

Sent from my iPhone

Begin forwarded message:

From: "Bodine, Susan" <bodine.susan@epa.gov>
Date: November 2, 2018 at 4:50:25 PM EDT
To: "Eby, Natasha" <eby.natasha@epa.gov>, "Humphreys, Hayly" <humphreys.hayly@epa.gov>, "Dickerson, Aaron" <dickerson.aaron@epa.gov>
Cc: "Starfield, Lawrence" <Starfield.Lawrence@epa.gov>, "Leff, Karin" <Leff.Karin@epa.gov>, "Dalzell, Sally" <Dalzell.Sally@epa.gov>, "Azad, Ava" <Azad.Ava@epa.gov>, "Wright, Peter" <wright.peter@epa.gov>, "Breen, Barry" <Breen.Barry@epa.gov>, "Cook, Steven" <cook.steven@epa.gov>, "Gervais, Gregory" <Gervais.Gregory@epa.gov>, "Orme-Zavaleta, Jennifer" <Orme-Zavaleta.Jennifer@epa.gov>, "Bussard, David" <Bussard.David@epa.gov>, "Leopold, Matt (OGC)" <Leopold.Matt@epa.gov>, "Fotouhi, David" <Fotouhi.David@epa.gov>, "Michaud, John" <Michaud.John@epa.gov>, "Strauss, Alexis" <Strauss.Alexis@epa.gov>, "Manzanilla, Enrique" <Manzanilla.Enrique@epa.gov>, "Herrera, Angeles" <Herrera.Angeles@epa.gov>
Subject: Background Materials for Tuesday Briefing on Ft. Edwards Dispute

Attached are background materials for the Tuesday, November 6 briefing for Acting Administrator Wheeler regarding the Ft. Edwards Air Force Base Superfund dispute.

Tuesday's briefing is to prepare Acting Administrator Wheeler for a not yet scheduled meeting with the Air Force and the State of California, to hear their arguments relating to the dispute.

This matter involves OECA, OLEM, OGC, ORD, and Region 9.

Susan

Susan Parker Bodine
Assistant Administrator
Office of Enforcement and Compliance Assurance
202-564-2440

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Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 3/2/2018 2:05:50 PM
To: Grevatt, Peter [Grevatt.Peter@epa.gov]
Subject: RE: Edwards AFB ROD amendment -

OK, should I call you at your desk?

From: Grevatt, Peter
Sent: Friday, March 02, 2018 9:05 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Edwards AFB ROD amendment -

Till the 9:30 with Dave.

From: Mclain, Jennifer
Sent: Friday, March 02, 2018 9:04 AM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Subject: RE: Edwards AFB ROD amendment -

Do you have time to discuss this morning? Attached is the background we have prepared for the meeting with OLEM on Monday.

From: Grevatt, Peter
Sent: Friday, March 02, 2018 8:46 AM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: RE: Edwards AFB ROD amendment -

Thanks. There are several important issues included in this message from Susan. I want to make sure we find an effective way to interface with Lee on this so we can stay on point.

From: Mclain, Jennifer
Sent: Thursday, March 01, 2018 5:23 PM
To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Subject: FW: Edwards AFB ROD amendment -

fyi

From: Forsgren, Lee
Sent: Thursday, March 01, 2018 3:19 PM
To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: Edwards AFB ROD amendment -

Let's talk about this.

Sent from my iPhone

Begin forwarded message:

From: "Bodine, Susan" <bodine.susan@epa.gov>
Date: March 1, 2018 at 2:34:50 PM EST
To: "Forsgren, Lee" <Forsgren.Lee@epa.gov>, "Ross, David P" <ross.davidp@epa.gov>
Cc: "Cook, Steven" <cook.steven@epa.gov>
Subject: RE: Edwards AFB ROD amendment -

Jim Woolford is handling.
I would also could talk to Steve Cook.

I don't know if OLEM is aware of OW's or ORD's work. I asked my Federal Facilities Enforcement people to reach out to OW and ORD, but I don't think they have done so. Who should I direct them to?

From: Forsgren, Lee
Sent: Thursday, March 1, 2018 2:11 PM
To: Bodine, Susan <bodine.susan@epa.gov>; Ross, David P <ross.davidp@epa.gov>
Subject: RE: Edwards AFB ROD amendment -

Susan,

I completely agree. That is especially true if we are going to make a determination not to regulate Perchlorate. Who should we talk to at OLEM on the matter? Kell?

Lee

From: Bodine, Susan
Sent: Thursday, March 1, 2018 1:56 PM
To: Ross, David P <ross.davidp@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>
Subject: Edwards AFB ROD amendment -

Air Force proposes to amend a Superfund Record of Decision to adopt to 6 ppm CA MCL for perchlorate based on a determination made in 2012 that the ROD cleanup level of 24 ppm was not protective of human health because it exceeded a hazard index of 1. There was political pressure from Boxer at the time to agree to CA's number.

I am worried about precedent if the Superfund program is saying 24 ppm is not protective. OW's current drinking water advisory is 15 ppb and that is the number SF currently uses. But you have work underway.

They also propose to change the TCE number to reflect a new (lower) IRIS value for TCE. I am less concerned about that.

They also want to change the PCE number since there is a new IRIS value that is higher than their number.

The NCP says we don't change cleanup levels to reflect new standards unless the old level is no longer protective.

Susan

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 3/2/2018 2:03:31 PM
To: Grevatt, Peter [Grevatt.Peter@epa.gov]
Subject: RE: Edwards AFB ROD amendment -
Attachments: Perchlorate OLEM Issue 3-1-18.docx

Do you have time to discuss this morning? Attached is the background we have prepared for the meeting with OLEM on Monday.

From: Grevatt, Peter
Sent: Friday, March 02, 2018 8:46 AM
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To: Grevatt, Peter <Grevatt.Peter@epa.gov>
Subject: FW: Edwards AFB ROD amendment -

fyi

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To: Mclain, Jennifer <Mclain.Jennifer@epa.gov>
Subject: Fwd: Edwards AFB ROD amendment -

Let's talk about this.

Sent from my iPhone

Begin forwarded message:

> **From:** "Bodine, Susan" <bodine.susan@epa.gov>
> **Date:** March 1, 2018 at 2:34:50 PM EST
> **To:** "Forsgren, Lee" <Forsgren.Lee@epa.gov>, "Ross, David P" <ross.davidp@epa.gov>
> **Cc:** "Cook, Steven" <cook.steven@epa.gov>
> **Subject: RE: Edwards AFB ROD amendment -**
>
> Jim Woolford is handling.
> I would also could talk to Steve Cook.
>
> I don't know if OLEM is aware of OW's or ORD's work. I asked my Federal Facilities Enforcement people to reach out to OW and ORD, but I don't think they have done so. Who should I direct them to?
>
> ---
>
> **From:** Forsgren, Lee
> **Sent:** Thursday, March 1, 2018 2:11 PM

To: Bodine, Susan <bodine.susan@epa.gov>; Ross, David P <ross.davidp@epa.gov>
Subject: RE: Edwards AFB ROD amendment -

Susan,

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Lee

From: Bodine, Susan
Sent: Thursday, March 1, 2018 1:56 PM
To: Ross, David P <ross.davidp@epa.gov>; Forsgren, Lee <Forsgren.Lee@epa.gov>
Subject: Edwards AFB ROD amendment -

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They also propose to change the TCE number to reflect a new (lower) IRIS value for TCE. I am less concerned about that.

They also want to change the PCE number since there is a new IRIS value that is higher than their number.

The NCP says we don't change cleanup levels to reflect new standards unless the old level is no longer protective.

Susan

Message

From: Schlosser, Paul [Schlosser.Paul@epa.gov]
Sent: 2/19/2019 12:57:04 PM
To: Hernandez-Quinones, Samuel [Hernandez.Samuel@epa.gov]
Subject: RE: perchlorate reports

Thanks. ☺

-Paul

From: Hernandez-Quinones, Samuel
Sent: Thursday, February 14, 2019 4:08 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: perchlorate reports

Hi Paul,

I have my team looking for these. As soon as I have any information I will forward to you.

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

"USEPA Protecting Human Health and the Environment"

From: Schlosser, Paul
Sent: Thursday, February 14, 2019 3:39 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: perchlorate reports

Sam,

I'm trying to find these two reports. Annie said they should be on a public CD somewhere, but I can't find them on the intranet.

Thanks,
-Paul

Yu, K.O., 2000. Consultative Letter from K.O. Yu to Annie Jarabek re: Tissue distribution and inhibition of iodide uptake in the thyroid by perchlorate with corresponding hormonal changes in pregnant and lactating rats (drinking water study). Department of the Air Force, Air Force Research Laboratory, Wright Patterson Air Force Base, AFRL-HE-WP-CL-2000-0038, June 28

Yu, K.O., 2002. Consultative Letter from K.O. Yu to Annie Jarabek re: Intravenous kinetics of radiolabeled iodide and perchlorate in tissues of pregnant and lactating Sprague-Dawley female rats dosed with perchlorate and/or

carrier free 125-I. Department of the Air Force, Air Force Research Laboratory, Wright Patterson Air Force Base, AFRL-HE-WP-CL-2002-0002, January 7

~~~~~~~~~~~~~~~~~~~~~~~

Paul M. Schlosser
NCEA, U.S. EPA
M.D. B243-01
RTP, NC 27711
T: 919-541-4130
F: 919-685-3330
E: schlosser.paul@epa.gov
~~~~~~~~~~~~~~~~~~~~~~~

Message

From: Hernandez-Quinones, Samuel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C46D56B82F143DF82F81D322BD109D7-HERNANDEZ-QUINONES, SAMUEL]
Sent: 2/14/2019 9:45:31 PM
To: Lauren Brown [Lauren_Brown@abtassoc.com]
CC: Ryan Klein [Ryan_Klein@abtassoc.com]
Subject: RE: Questions on Derivation

Ok.

Great thanks.

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

"USEPA Protecting Human Health and the Environment"

From: Lauren Brown <Lauren_Brown@abtassoc.com>
Sent: Thursday, February 14, 2019 4:40 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Ryan Klein <Ryan_Klein@abtassoc.com>
Subject: RE: Questions on Derivation

Hi Sam:
I do not have them. I did some quick google searching, searched EPA's hero database and used the document #s to search the federal register and could not find the PDFs. I can ask our librarian to see if she could somehow locate them and get back to you.

Thanks
Lauren

Lauren Brown | Associate/Scientist | Abt Associates
O: 301.347.5832 | F: 301.828.9859 | www.abtassociates.com

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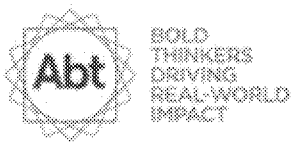

From: Hernandez-Quinones, Samuel [mailto:Hernandez.Samuel@epa.gov]
Sent: Thursday, February 14, 2019 4:04 PM
To: Lauren Brown <Lauren_Brown@abtassoc.com>

Cc: Ryan Klein <Ryan_Klein@abtassoc.com>
Subject: RE: Questions on Derivation

Hi Lauren thanks for your input.

Also, I don't know if you have any copies of the two documents referenced below but if you do could you please send to me.

Thanks
Sam

Yu, K.O., 2000. Consultative Letter from K.O. Yu to Annie Jarabek re: Tissue distribution and inhibition of iodide uptake in the thyroid by perchlorate with corresponding hormonal changes in pregnant and lactating rats (drinking water study). Department of the Air Force, Air Force Research Laboratory, Wright Patterson Air Force Base, AFRL-HE-WP-CL-2000-0038, June 28

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

"USEPA Protecting Human Health and the Environment"

From: Lauren Brown <Lauren_Brown@abtassoc.com>
Sent: Thursday, February 14, 2019 11:50 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Ryan Klein <Ryan_Klein@abtassoc.com>
Subject: RE: Questions on Derivation

Hi Sam:
The person asking the questions has properly interpreted the information presented in the MCLG derivation document. You can tell them they do have it right. Let us know if there are further questions.

Lauren

Lauren Brown | Associate/Scientist | Abt Associates
O: 301.347.5832 | F: 301.828.9859 | www.abtassociates.com

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From: Hernandez-Quinones, Samuel [mailto:Hernandez.Samuel@epa.gov]
Sent: Thursday, February 14, 2019 11:12 AM
To: Lauren Brown <Lauren_Brown@abtassoc.com>
Subject: Questions on Derivation

Hi Lauren,

I need some support in responding to questions I received about the derivation of the MCLG. Please see the questions below and let me know if you can provide some responses/ context for these.

Thanks
Sam

I was hoping to get clarification of the DWI and RSC age range discussion. I've read both the discussion in the FR and the discussion in the background document. Do I have this right?

- To calculate the MCLG, OW used DWI corresponding to women of childbearing age, rather than pregnant or lactating women, because the analysis used in deriving the RSC (food exposure) was performed for WCBA. "The EPA chose to use exposure factor estimates specific to women of childbearing age in deriving an MCLG (i.e., non-pregnant, non-lactating, 15–44 years of age). This determination was reached as the analysis in the development of an RSC was performed using a population of women of childbearing age from NHANES (20 – 44 years of age)."

- The RSC analysis defined WCBA as 20-44 because that was how WCBA were defined in the BBDR modeling. "The EPA acknowledges there is a difference in the age group defining women of child bearing age used to develop the drinking water intake rate compared to what is used to develop the relative source contribution, which was based on the age group used in developing the BBDR model."

- The WCBA age range for DWI does not match the WCBA age range for the RSC (and used in the BBDR model), because the DWI estimate is based on the analysis presented in the EFH which defines WCBA as age 15-44. "However, the EFH reports this drinking water intake to be applicable for women of childbearing age, and the age range of the BBDR model fits within the age range used to estimate this recommended drinking water intake."

==========

Samuel Hernández Quiñones, P.E.
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Office of Water
Environmental Protection Agency
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Washington, DC 20460
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"USEPA Protecting Human Health and the Environment"

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Message

From: Hernandez-Quinones, Samuel [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C46D56B82F143DF82F81D322BD109D7-HERNANDEZ-QUINONES, SAMUEL]
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"USEPA Protecting Human Health and the Environment"

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Sent: Thursday, February 14, 2019 11:50 AM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Ryan Klein <Ryan_Klein@abtassoc.com>
Subject: RE: Questions on Derivation

Hi Sam:
The person asking the questions has properly interpreted the information presented in the MCLG derivation document. You can tell them they do have it right. Let us know if there are further questions.

Lauren

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Message

From: Huff, Lisa [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9B92A21924BE488994A5C7BDF23F79FE-LHUFF02]
Sent: 3/8/2017 8:51:21 PM
To: Russell, Meredith [Russell.Meredith@epa.gov]
Subject: FW: PFAS - Bill would force EPA to set limits on industrial chemicals (E&E Daily)

fyi

Lisa Foersom Huff

Associate Branch Chief
Targeting and Analysis Branch
Standards and Risk Management Division
Office of Groundwater and Drinking Water
U.S. EPA
EPA East Bldg. Rm. 2357 H
202-566-0787

From: Flowers, Lynn
Sent: Wednesday, March 08, 2017 12:38 PM
To: Geroux, Nicholas <Geroux.Nicholas@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Foster, Stiven <Foster.Stiven@epa.gov>; Raffaele, Kathleen <raffaele.kathleen@epa.gov>; Benson, Amy <Benson.Amy@epa.gov>; Benson, Bob <Benson.Bob@epa.gov>; Lambert, Jason <Lambert.Jason@epa.gov>; Noyes, Pamela <Noyes.Pamela@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Crofton, Kevin <Crofton.Kevin@epa.gov>; Gaines, Linda <Gaines.Linda@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Scozzafava, MichaelE <Scozzafava.MichaelE@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>; Carter, Bobbi <Carter.Bobbi@epa.gov>; Hasan, Jafrul <Hasan.Jafrul@epa.gov>; OBrien, Wendy <OBrien.Wendy@epa.gov>; Patlewicz, Grace <Patlewicz.Grace@epa.gov>; Chang, Daniel <chang.daniel@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Donohue, Joyce <Donohue.Joyce@epa.gov>; Lau, Chris <Lau.Christopher@epa.gov>; Cooke, Maryt <Cooke.Maryt@epa.gov>; Buckley, Timothy <Buckley.Timothy@epa.gov>; Strynar, Mark <Strynar.Mark@epa.gov>; Lindstrom, Andrew <Lindstrom.Andrew@epa.gov>; Cooperstein, Sharon <Cooperstein.Sharon@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Impellitteri, Christopher <Impellitteri.Christopher@epa.gov>
Subject: PFAS - Bill would force EPA to set limits on industrial chemicals (E&E Daily)

From: Kavlock, Robert
Sent: Wednesday, March 08, 2017 12:31 PM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>
Subject: FW: News Update: Bill would force EPA to set limits on industrial chemicals (E&E Daily)

From: Frithsen, Jeff
Sent: Wednesday, March 08, 2017 11:20 AM
To: Kavlock, Robert <Kavlock.Robert@epa.gov>; Rodan, Bruce <rodan.bruce@epa.gov>
Subject: FW: News Update: Bill would force EPA to set limits on industrial chemicals (E&E Daily)

Since a briefing on PFAST is under development, thought this might be of interest.

I'm assuming you will get this from multiple sources.

Jeff

Bill would force EPA to set limits on industrial chemicals

Cecelia Smith-Schoenwalder, E&E News reporter
March 06, 2017

New York Democratic Sens. Chuck Schumer and Kirsten Gillibrand introduced a Senate bill yesterday that would require U.S. EPA to set Safe Drinking Water Act limits on perfluorinated compounds and other chemicals used in firefighting foam and the manufacturing of Teflon cookware, plastics and fabrics.

Their legislation, **S. 519**, calls for standards for perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), 1,4-dioxane and perchlorate. PFOA and PFOS have been linked to cancer and birth defects.

"We've seen very clearly how much damage can happen to our local drinking water supplies when toxic chemicals like PFOA, PFOS, 1,4 dioxane, and perchlorate aren't monitored by the EPA," Gillibrand said in a statement.

Rural communities in New Hampshire, New York and Vermont are wrestling with the spread of PFOA in groundwater (***Greenwire***, May 20, 2016).
PFOA in the Hoosick Falls, N.Y., water supply spurred the state Senate last month to recommend creating a new state regulatory body. New York Gov. Andrew Cuomo's (D) response to the contamination has been faulted by environmentalists (***Greenwire***, Nov. 22, 2016).

Scott Faber, senior vice president of the Environmental Working Group, expressed support for Schumer and Gillibrand's legislation in a statement.

"If President Trump is serious about providing 'crystal clear, clean drinking water' to all Americans, he should leap at the chance to sign this legislation," Faber said. "Congress can and must take action to reduce the public's exposure and it can start by passing this legislation."

Schumer said "we can never be too safe" when it comes to drinking water.

"I will use every ounce of my clout to work with my colleagues in the Senate and make sure this common-sense public health bill to ensure safe drinking water is passed," his statement continued.

PFOA and PFOS were used in firefighting foam by the Air Force for decades. States like New York have had Superfund sites declared at bases where the foam was used (***Greenwire***, Jan. 31).

Message

From: EPA Federal Register [envsubset@epa.gov]
Sent: 7/21/2020 1:37:28 PM
To: Federal Register documents [epafr-all@lists.epa.gov]
Subject: [epafr-all] Table of Contents, July 21, 2020

A single listserv is used to send a copy of the Federal Register table of contents to each of the previous list subscribers. The e-mail includes links and topic tags for the notices that were previously included in the Environmental Subset Web site and topical listservs. It also includes the table of contents for the Federal Register of that day. Subscribers no longer receive the full-text of FR notices. The official source for the electronic Federal Register is the Government Printing Office (https://www.govinfo.gov/app/collection/FR/). More information is also available from Regulations.gov (http://www.regulations.gov/).

AIR

Air Quality State Implementation Plans; Approvals and Promulgations: South Carolina and Tennessee: Minimum Reporting Requirements in State Implementation Plans, 44027-44031
https://www.govinfo.gov/content/pkg/FR-2020-07-21/html/2020-15720.htm
https://www.govinfo.gov/content/pkg/FR-2020-07-21/pdf/2020-15720.pdf

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Consult the Reader Aids section at the end of this issue for phone numbers, online resources, finding aids, and notice of recently enacted public laws.

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Message

From: Olson, Daniel [Olson.Daniel@epa.gov]
Sent: 8/10/2017 2:02:45 PM
To: Huff, Lisa [Huff.Lisa@epa.gov]
Subject: FW: Perchlorate Workgroup

Perchlorate Workgroup:

Yesterday we continued our discussions with OMB and our interagency partners on the perchlorate peer review. Please find attached for your information the materials we transmitted to the meeting participants:

- A revised draft peer review charge that incorporates the input we have received to this point;
- A briefing document that presents information on our evaluation with a focus on the review of studies to assess the relationship between thyroid hormone changes and neurodevelopmental outcomes; and
- A table from the draft report that characterizes the studies identified as having data relating thyroid hormone levels to neurodevelopmental outcomes.

We're nearing completion of the draft MCLG Approach Report. When we get the green light, we intend to have a contractor conduct an independent, external peer review of the report this fall. Next steps are found in the attached briefing.

Key topics

1. Continuation of the discussion on the process for identifying literature
2. Revised charge based on interagency comments
3. Preliminary draft findings

Next steps

1. revise charge based on mtg input (e.g., line edits/clarity)
2. send revised charge to OMB/interagency partners/workgroup (courtesy) early next week
3. comments due end of next week (8/18)
4. re-initiate peer review effort (e.g., revise FRN pkg, check availability peer review candidates)
5. finalize draft report (2 weeks, 8/25?)

From: Olson, Daniel
Sent: Wednesday, July 19, 2017 10:58 AM
To: Benson, Bob <Benson.Bob@epa.gov>; Cantilli, Robert <Cantilli.Robert@epa.gov>; Chiu, Enid <Chiu.Enid@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Collantes, Margarita <Collantes.Margarita@epa.gov>; Crofton, Kevin <Crofton.Kevin@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>; El Burai Felix, Alia <elburaifelix.alia@epa.gov>; Firestone, Michael <Firestone.Michael@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Foos, Brenda <Foos.Brenda@epa.gov>; Georges, Jessica <Georges.Jessica@epa.gov>; Gilbert, Mary E. <Gilbert.Mary@epa.gov>; Hafez, Ahmed <Hafez.Ahmed@epa.gov>; Harmon, Kenneth <Harmon.Kenneth@epa.gov>; Helm, Erik <Helm.Erik@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Johnson, Ann <Johnson.Ann@epa.gov>; Jones, Joel E. <Jones.Joel@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Kirk, Andrea <Kirk.Andrea@epa.gov>; Li, Corine <Li.Corine@epa.gov>; Macler, Bruce <Macler.Bruce@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Morrison, Kendra <Morrison.Kendra@epa.gov>; Olson, Daniel <Olson.Daniel@epa.gov>; 'Paul Schlosser' <schlosser.paul@epa.gov>; Perkinson, Russ <Perkinson.Russ@epa.gov>; Raffaele, Kathleen <raffaele.kathleen@epa.gov>; Schutz, Michelle <Schutz.Michelle@epa.gov>; 'Sharon Cooperstein' <cooperstein.sharon@epa.gov>; Skaar, Christina <Skaar.Christina@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Townsend, Clifton <Townsend.Clifton@epa.gov>

Cc: Huff, Lisa <Huff.Lisa@epa.gov>
Subject: Perchlorate Workgroup

Perchlorate Workgroup:

Today's perchlorate workgroup meeting is cancelled.

Below is a summary yesterday's briefing.

On July 18, at the request of OMB, ORD and OW provided an overview of 1) the peer reviewed perchlorate biologically based dose-response model, 2) peer review recommendations, 3) model revisions, and 4) MCLG approaches for deriving a perchlorate MCLG to OMB and our interagency partners. Invitees included HHS; DOE; Air Force, Army; SBA and NASA. (Slide deck and charge is attached.) As you recall, our draft approach demonstrates relationships between thyroid hormone levels (BBDR model output) and neurodevelopmental effects for peer reviewed studies.

The topics discussed include using a weight of evidence approach for the peer reviewed studies; using a meta-analysis approach to formulate the basis of our decision and several invitees requested a copy of the draft report. EPA agreed to provide attendees a table of results. We'll also send the table to the workgroup once drafted.

We're nearing completion of the draft MCLG Approach Report. When we get the green light, we intend to have a contractor conduct an independent, external peer review of the report this fall. Next steps are found in the attached briefing.

Thanks,

Dan

Office of Research and Development

Human Health Risk Assessment

Products and Outputs in FY18

March 6, 2019

Science Assessments Delivered Across HHRA's Portfolio

Human Health Risk Assessment

FINAL CHEMICAL ASSESSMENTS ACROSS THE PORTFOLIO

- Final Integrated Science Assessment for Sulfur Oxides - Health Criteria
- Final IRIS Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
- Four Provisional Peer-Reviewed Toxicity Value Assessments
  - Stable (Nonradioactive) Gadolinium
  - Stable (Nonradioactive) Soluble Lutetium
  - Stable (Nonradioactive) Soluble Lanthanum
  - Technical Toxaphene, Weathered Toxaphene, and Toxaphene Congeners

Human Health Risk Assessment

ASSESSMENT SCOPING AND PLANNING

Systematic Review Protocol for the IRIS Chloroform Assessment (Inhalation)

- Reflects the methods for conducting a systematic review of the available scientific literature

IRIS Assessment Plans for Naphthalene, Ammonia, and Uranium

- Reflect the IRIS Program's initial scoping and problem formulation results

- Due to IRIS Prioritization, these assessment will not move forward at this time. A list of assessments prioritized for FY2019 can be found here: IRIS Outlook.

Human Health Risk Assessment

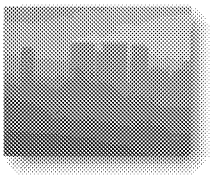
Science Assessment Translation and Technical Support

Integrated Science Assessments (ISA) and Scientific/Regulatory Support

SCIENTIFIC AND REGULATORY SUPPORT FOR THE NAAQS

CONTACT: STEVE DUTTON (NCEA-RTP)

Description: HHRA provided sustained and substantial scientific and technical support to OAR and OGC supporting the various steps in the National Ambient Air Quality Standards review process for Oxides of Sulfur – Health Criteria, Particulate Matter, Ozone, Oxides of Nitrogen – Health Criteria, and Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter – Ecological Criteria.



Purpose and Research Approach: HHRA scientists are subject matter experts for the science supporting the NAAQS. Beyond development of the Integrated Science Assessments, NCEA provides scientific and technical support for:

(1) Risk and Exposure Assessment (REA)
(2) Policy Assessment (PA)
(3) Notice of Proposed Rulemaking (NPR)
(4) Response to Comments document (RTC)
(5) Provisional study evaluation
(6) Final rulemaking support
(7) Litigation and decision support

Impact and Use: HHRA's support ensures the scientific rigor and legal defensibility of the NAAQS.

Community and Site-Specific Risk

SUPERFUND HEALTH RISK TECHNICAL SUPPORT CENTER (STSC) AND ECOLOGICAL RISK ASSESSMENT SUPPORT CENTER (ERASC)

CONTACT: TERESA SHANNON / BETH OWENS (NCEA-CIN)

Description: Through the STSC and ERASC, HHRA provides scientific technical support in the area of human health and ecological risk assessment of contaminated sites to EPA's program offices and regions supporting Superfund, Resource Conservation & Recovery Act (RCRA), and Brownfield sites.

Purpose and Research Approach: The TSCs responded to requests for specialized technical assistance. The STSC provided support for OLEM and Regions 1, 2, and 5 by responding to over 25 requests for technical support including:

- review of the evidence relevant to the toxicokinetics and health effects following dermal or inhalation exposure to PFAS compounds, and
- requests to evaluate the suitability of proposed surrogates for chemicals of interest at Superfund sites with no available toxicity values

Impact and Use: HHRA's support ensures communities faced with an urgent need are provided coordinated assistance to assess and address issues of chemical and other environmental contamination.

Human Health Risk Assessment

HUMAN HEALTH SUPPORT TO EPA PROGRAM OFFICES AND REGIONS

CONTACT: KRIS THAYER (NCEA-IRIS)

Description: HHRA provided more than 500 hours of technical support to a number of program offices and regions, including support for:

- Perchlorate PBPK/PD or BBDR modeling and analyses for Office of Water
- TSCA Implementation and Risk Evaluation Support for Office of Toxics and Pollution Prevention
- Chloroprene PBPK expertise for Office of Air and Radiation, Region 6, and State of Louisiana

Purpose and Research Approach: Scientists in HHRA are leaders in the science of human health hazard and dose-response assessment. Expertise housed in HHRA (e.g., pharmacokinetic modeling, statistics, systematic review, neurotoxicology) is critical to supporting States, program and regional office activities. HHRA provides technical expertise upon request from EPA Programs and regions on an ad-hoc basis.

Impact and Use: HHRA technical support assists EPA program and regional office regulatory decision-making.

Human Health Risk Assessment

SYSTEMATIC REVIEW TRAINING AND PARTNERSHIPS

CONTACT: KRIS THAYER (NCEA-IRIS)

Description: Systematic review plays an important role in enhancing scientific rigor and transparency. HHRA is developing tools and partnerships with highly trained, diverse professionals in science, technology, engineering, and mathematics (STEM) fields.

Purpose: HHRA is pursuing innovative partnerships and other opportunities to address, engage, and tackle complex challenges facing the Program, including in applying systematic review methods to chemical assessments.

Research Approach: Partnerships within the human health risk assessment field are being built through the EPA-wide Systematic Review Communities of Practice, public workshops, targeted hands on training with state agencies who conduct chemical assessments, and memorandums of understanding and interagency agreements with academic and Federal partners.

Impact and Use: Ensures the HHRA systematic review methods and approaches are more efficient and applicable to the broader systematic review community.

Innovations in Assessment Science and Development

Integrated Risk Information System (IRIS) and Regulatory Support

INNOVATION IN CONDUCTING SYSTEMATIC REVIEW IN HUMAN HEALTH ASSESSMENTS

CONTACT: KRIS THAYER (NCEA-IRIS)

Description: HHRA developed and disseminated innovative workflow methods and processes for implementing systematic review via the IRIS Handbook and presentations, meetings, and training sessions with internal and/or external stakeholders.

Purpose: Systematic review plays an important role in enhancing scientific rigor and transparency. Well-defined procedures, templates, and training ensures consistent and efficient application of the HHRA systematic review approach throughout assessment development.

Research Approach: "Handbook for Developing IRIS Assessments," or IRIS Handbook, provides operating procedures to the scientists in the IRIS Program for when developing draft IRIS assessments.

Impact and Use: Ensures understanding of the approaches used to evaluate the human health hazards from exposure to chemicals in the environment and underpin the scientific conclusions contained within each assessment.

Community and Site-Specific Risk

ANALYZING GREENSPACE AND ALLERGY OCCURRENCE FROM A CUMULATIVE RISK ASSESSMENT (CRA) PERSPECTIVE

CONTACT: GLENN RICE (NCEA-CIN)

Description: This manuscript highlights the potential importance of using high-resolution greenspace measures that distinguish between tree- and grass-covered areas.

Purpose and Research Approach: Residential proximity to urban greenspace (GS) has been linked to multiple health benefits in children, including improved cognitive functioning and physical activity. The evidence is less clear regarding impacts of GS on childhood allergic disease including sensitization to aeroallergens and development of allergic rhinitis.

Impact and Use: This study provides insight to risk managers including urban planners regarding the potential health benefits of urban greenspaces. The manuscript also suggests that health impacts in children may depend on the type of vegetation covering the greenspace.

R. Gernes, C. Brokamp, G. Rice, J. Wright, M. Kondo, Y. Michael, G. Donovan, D. Gatziolis, D. Bernstein, G. LeMasters, J. Lockey, G. Hershey, P. Ryan. Using high-resolution residential greenspace measures in an urban environment to assess risks of allergy outcomes in children

Advancing Analyses and Applications

APPLICATION OF A TIERED SURROGATE APPROACH IN SUPPORT OF QUANTITATIVE HUMAN HEALTH RISK ASSESSMENT OF ORGANOCHLORINE CONTAMINANTS

CONTACT: LUCINA LIZARRAGA (NCEA-CIN)

Description: Describes a real case study example on the application of a read-across methodology to support screening-level assessment of an environmental contaminant detected at an EPA Superfund site, lacking sufficient information for risk assessment via conventional practices.

Purpose and Research Approach: Provides a practical example of the utility and application of read-across and other new approach methodologies (NAMs) for the derivation of screening-level health reference values for repeated dose toxicity.

Lizarraga, LE; Dean, JL; Kaiser, JP; Wesselkamper, SC; Lambert, JC; Zhao, QJ. 2018. A Case Study on the Application of An Expert-driven Read-Across Approach in Support of Quantitative Risk Assessment of p,p'-Dichlorodiphenyldichloroethane.

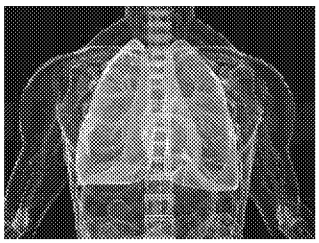
Impact and Use: Helps advance research efforts towards the implementation and acceptance of NAMs and alternative data streams in human health risk assessment with the potential to fill regulatory data gaps and assist in chemical-specific cleanups across the U.S. and other Agency-wide activities.

Advancing Analyses and Applications

ADVANCEMENTS IN INHALATION DOSIMETRY

CONTACT: ANNIE JARABEK (NCEA-RTP)

Description: HHRA made advancements in the area of inhalation dosimetry through publications on:



- Advancement of *in vitro* methods to address acute inhalation testing requirements: https://www.ncbi.nlm.nih.gov/pubmed/29277654
- Development of a decision strategy for applying NAMs to inform assessment of inhalation exposures: https://www.ncbi.nlm.nih.gov/pubmed/29908304
- Characterization of important dosimetry determinants for inhalability, deposition and retention of elongate mineral particles (EMPs): https://www.ncbi.nlm.nih.gov/pubmed/29738812

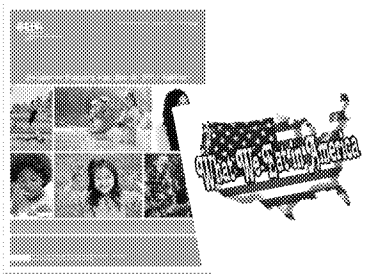
Impact and Use: This research addresses the challenges of translation and evidence integration posed by inhalation exposures for human health risk assessment by advancing best practices for the use of new approach methodologies (NAMs) and dosimetry modeling to inform in vitro to in vivo extrapolation (IVIVE) and their application to integrated testing and assessment approaches (IATA).

Advancing Analyses and Applications

ADVANCEMENTS IN EXPOSURE

CONTACT: LINDA PHILLIPS (NCEA-DC)

Description: HHRA made advancements to the application of exposure sciences by releasing tools and updates to the primary source of exposure factor information necessary for exposure assessments.



Research Approach: HHRA provided information to exposure scientists through:

- Updated five chapters of the Exposure Factors Handbook
- Released the Food Commodity Intake Database (FCID) Consumption Calculator
- Released EPA's Ecological Risk Assessment ToolBox (EPA EcoBox)

Impact and Use: These materials may be used by scientists, economists, and other interested parties as a source of data and/or U.S. EPA recommendations on numeric estimates for behavioral and physiological characteristics needed to estimate exposure to environmental agents.

Human Health Risk Assessment

Essential Assessment Infrastructure Advancements

Advancing Analyses and Applications

INTEGRATION AND INTEROPERABILITY OF HEALTH AND ENVIRONMENTAL RESEARCH ONLINE (HERO) WITH OTHER SYSTEMATIC REVIEW TOOLS

CONTACT: STEVE DUTTON (NCEA-RTP)

Description: Health and Environmental Research Online (HERO) is part of the open government directive to conduct business with transparency, participation, and collaboration. Tools have been developed and integrated within HERO to assist with assessment development and systematic review across multiple EPA Offices.

Purpose and Research Approach: HERO has significantly improved interoperability between third party tools and core HERO components by developing an Application Programming Interface (API) and by developing workflows that allow for efficient transfer of data between HERO and third party tools.

Impact and Use: HERO's focus on improving interoperability will result in increased efficiency, while retaining transparency and reliability. These advancements have made products developed through HERO more versatile, nimble and responsive, as we have been able to capitalize on the strengths and capabilities of third party systematic review tools.

Advancing Analyses and Applications

BENCHMARK DOSE SOFTWARE (BMDS) 3.0 RELEASED

CONTACT: JEFF GIFT (NCEA-RTP) AND ALLEN DAVIS (NCEA-CIN)

Description: Benchmark Dose Software (BMDS) is the primary dose-response tool for use in human health risk assessments within the EPA and globally with well over 5,000 registered users across 90 countries. This year HHRA released BMDS 3.0

Purpose and Research Approach: The application of BMD methods invokes scientific and practical challenges associated with modeling dose-response data and interpreting the modeling results. The BMDS 3.0 interface has been designed to facilitate performing, interpreting and tracking dose-response analyses of multiple dichotomous, combined tumor, nested dichotomous, and continuous response datasets. Key components of BMDS 3.0 have been added to address the challenges of dose-response modeling such as data limitations and model uncertainty Bayesian modeling and model averaging

Impact and Use: BMDS 3.0 enhances the state-of-the-science in dose-response modeling methods to derive more accurate/reliable PODs, streamline BMD processes, harmonize U.S. and European methods, and pave the way for future BMDS enhancements.

THANK YOU!

Message

From: Dourson, Michael [dourson.michael@epa.gov]
Sent: 1/4/2018 1:26:49 PM
To: Pruitt, Scott [Pruitt.Scott@epa.gov]
CC: Ford, Hayley [ford.hayley@epa.gov]; Jackson, Ryan [jackson.ryan@epa.gov]
Subject: Next steps

Dear Administrator Pruitt

I deeply appreciate the opportunity to work in your EPA. It was humbling to get back, if only briefly, and to again participate in the work of this great organization. As you know, I will be working in Ohio over the next several weeks and going through a Jesuit discernment to determine where God best sees my talents being used. Your thoughts on this would be welcome.

EPA will be faced with numerous difficult decisions over the next several months. Many of these decisions will involve the determination of the safe, or virtually safe, dose of chemicals such as formaldehyde, chlorpyrifos, chromium, glyphosate, dioxane, TCE and perchlorate. Toxicologists in EPA that are in the best positions to advise you on these and other chemicals include:

- Nancy Beck, Deputy AA OSCPP. She is board certified and well respected in numerous circles. Her grasp of rules and regulations from her time at OMB is proving invaluable.
- Edward Ohanian, Associate Director for Science OW. He is a winner of the Society of Toxicology (SOT) Lehman Award (sort of like the Nobel prize for risk assessment), and is well respected nationally and internationally. He is also the current president of SOT's specialty section for regulatory and safety evaluation.
- Rory Conolly, Senior Research Biologist ORD. He is also a winner of the Society of Toxicology (SOT) Lehman Award and is well respected nationally and internationally. He is well published in the area of formaldehyde risk assessment.
- Annie Jarabek, Inhalation toxicologist ORD. She is a winner of the Society for Risk Analysis Risk Practitioner award, and is well respected nationally and internationally. She is the single best inhalation, risk assessment toxicologist in the US. EPA is fortunate to have her.
- John Lipscomb. Senior Toxicologist Homeland Security-ORD. He was a nominee for President of the Society of Toxicology (SOT), which indicates the respect he has among his peers, and is well respected nationally and internationally. He is well published in the area of TCE risk assessment.

Of course, you should feel free to call me at any time. I am at your and His service.

Cheers!

Michael...

... L. Dourson, PhD., DABT, FATS, FSRA
Senior Advisor to the Administrator
U.S. Environmental Protection Agency

dourson.michael@epa.gov
202-564-2463
www.epa.gov

Ex. 6 Personal Privacy (PP)