

**Comments from Members of the SAB Perchlorate Advisory Panel on the
draft (9/5/2012) panel report, Advice on Approaches to Derive a
Maximum Contaminant Level Goal for Perchlorate**

(As of September 24, 2012)

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Dr. Grant W. Anderson

Page 3 Line 25-30. Summary is well stated.

Page 7 Line 1-12. Well summarized and captures our perspective.

P 7 Line 26-27. Add citation. Paediatr Perinat Epidemiol. 2012 Jul;26 Suppl 1:108-17. doi: 10.1111/j.1365-3016.2012.01275.x. **The effects of iodine deficiency in pregnancy and infancy.** Zimmermann MB.

P8 L3 Add citation. Environ Health Perspect. 2008 Jun;116(6):752-60. **Developmental exposure to perchlorate alters synaptic transmission in hippocampus of the adult rat.** Gilbert ME, Sui L.

Page 8 Line 7. I'm having a difficult time finding a citation for this statement. It seems obvious but not easily determined/measured.

Page 9 Line 36- 40 Looking for additional citations. We need to state what these methodological limitations are. I think Nancy can best articulate these limitations, which include a lack of adequate consideration of iodine stores in the thyroid gland. If the perchlorate studies are too short-term the iodine and thyroid hormone stores in the thyroid will not be depleted for perhaps up to several weeks. Therefore short-term perchlorate challenge would be unlikely to perturb thyroidal function as measured by serum thyroid hormones and TSH and also iodide uptake. Longer-term challenge would be necessary to adequately assess the impact of perchlorate exposure on iodide uptake by the human adult thyroid gland. This is a criticism of the Greer study due to the short term nature of the study. In addition, these are ADULT non-pregnant subjects. Extrapolation to pregnant women, children, neonates and fetuses can only be done with great caution.

Page 11 Line 25- 27 Should we be more specific here and list what these limitations specifically are?

Page 11 Line 29- 33 This is a summary of above. Do we need additional citations here?

Page 11 Line 37-42 We can/should provide more clarity here . The overview is great but we are not really recommending anything here other than to consider a variety of issues regarding future studies.

The literature on the immediate and long-term impact of iodine insufficiency on the developing fetus are very robust for both humans and for animal models. The existing literature on the effects of maternal perchlorate exposure on the developing fetus are considerably less robust, especially the impact on the human fetus. As the known biological impact of perchlorate exposure is functionally equivalent to iodine deficiency in the thyroid gland, we recommend using available iodine insufficiency data as a surrogate for perchlorate exposure in the development of predictive models of perchlorate exposure on fetal health. We recognize that using surrogate data carries inherent risk and therefore we strongly recommend additional

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studies, in both humans and animal models, focused on determining the impact of perchlorate on thyroid hormone economy in the pregnant female and fetus.

Page 12 Line 7-19 In regard to these specific experimental add-ons I don't know who we are recommending do these studies. I don't think we can recommend a specific group do this work. I'm unclear if we should include these specific recommendations here (a-e). The general recommendations below are fine. Can these recommendations be included as an appendix item? I'm not even sure we should do that though. We should discuss in the committee.

Page 12 Line 21-27 To clarify this recommendation, the need is that many of the currently published studies are missing some key elements important for fully testing the hypotheses. We are recommending that when future studies are conducted (which we are recommending should be performed as we need more robust data to develop strong predictive models) the investigators consider these additional parameters. These specific recommendations can be incorporated into both animal and human studies. No recommendations about who should carry these studies out.

Page 16 Line 9-20. Are the modeling experts OK with the human iodide uptake inhibition in humans data? Is it sufficient to develop a robust model? Should there be a recommendation to gather further data as there are limitations in the currently available human data - especially in vulnerable populations?

P 21 Line 23-27. I don't understand this sentence. Did we discuss this?

P 22 Line 1-2. Will get these citations. However the definitions do vary. May need to alter language - "for example, defined as ...

P 22 Line 6 regarding the sensitive life stages their fetuses and infants also lactating women to Hypothyroxinemic Pregnant women

P 22 Line 14 same comments regarding the sensitive life stages women, their fetuses and infants.

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Dr. Hugh A. Barton

General Comments

Overall the report is well done and provides useful information and generally clear recommendations. It provides subtleties of direction that extend the NRC report perspective (e.g., the focus on hypothyroxinemia) and provide EPA strategy for deriving an MCLG.

If it is desired to be more explicit about the approach to developing an MCLG, several options are possible depending in part of the time frame that EPA feels is relevant and the resources they have available. As stated in the report, the longest term option would be to extend the PBPK/PD-IUI model to include both thyroid hormone levels and consequent effects on neurodevelopment (based upon iodide deficiency literature), which would also involve addressing dietary iodide intake at the different life stages and thus, both people with adequate and iodide deficient intakes. An intermediate option, is to extend the model to include thyroid hormone production, which again would involve addressing dietary iodide intake and thus, both people with adequate and iodide deficient intakes. In this approach, one would then develop an empirical relationship likely from the iodide deficiency literature to describe changes in hormones and their linkage to neurodevelopmental outcomes for purposes of selecting an adverse effect level to protect against. A nearer term option would be to utilize the existing PBPK/PD-IUI model to predict inhibition of iodide uptake from drinking water at different ages. Steps between uptake inhibition and neurodevelopmental outcomes would then need to be described using relationships for each step based upon literature data. One might develop an empirical relationship between iodide uptake inhibition and urinary iodide levels (e.g., is a 2% inhibition equivalent to a 2% decrease in urinary iodide), such that one could use the relationship between urinary iodide and thyroid hormones levels as described, for example, in Silva and Silva (1981). One would then link hormone levels and neurodevelopmental changes. If this doesn't appear feasible near term, EPA might choose to select a level of inhibition they feel is consistent with the NAS recommendations, which focused upon ~2% inhibition as being not statistically differentiable. The argument in the NAS report was that ensuring that uptake inhibition was limited would limit adverse neurodevelopmental changes. Thus, they recommended use of a 10-fold uncertainty factor to protect sensitive subpopulations or life stages, which could be interpreted in the MCLG context as indicating that EPA needed to ensure limited uptake inhibition as predicted by the PBPK/PD-IUI model for the appropriate life stages. It is worth noting, that while there is a focus in terms of neurodevelopmental effects in iodide intake deficient individuals, there is no literature currently identified that indicates that such individuals would have different radioactive iodide uptake inhibition, so the current model could be considered (an assumption) to address both individuals with sufficient and insufficient iodide status. This would explicitly change when modeling thyroid hormone levels as then iodide status would explicitly be incorporated in the model for events after iodide transport.

There is a tendency throughout the document to state that the presence of perchlorate leads to inhibition of iodide uptake and thus thyroid hormone biosynthesis as if this was independent

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upon perchlorate levels (e.g., a hazard identification type of statement rather than a dose-response perspective). It would be appropriate to edit such text and some are noted below in specific comments.

Specific Comments

Letter p 1 line 32: Make “Contaminants” singular.

Letter p2 line 4: insert “hormone” between “thyroid” and “homeostasis”. Insert “function” or “hormone levels” after “Interference with thyroid”.

Letter p 2 line 13: insert “(PBPK/PD)” before “modeling” as the abbreviation is used in the next paragraph undefined.

P 4 line 19: add () around RAIU

P 7 line 15: reword as “...by their distinctive structures with three or four iodine atoms respectively attached...”

P 7 line 43: Reword to acknowledge dose-response relationships, e.g., “...in the presence of increasing perchlorate, less iodide is available...” or “...in the presence of perchlorate, less iodide may be available for TH biosynthesis.”

P 8 line 3: Is the animal data with perchlorate on neurodevelopmental effects just “suggestive”? (see p 11 line 7-8, which seems more strongly worded)

P 8 lines 20-21: “are likely identical” seems a strong statement if the “pharmaco-active substances” are chemically unrelated drugs. Could it be replaced with “Perchlorate pharmacokinetics and its inhibition of iodide uptake are also likely subject to developmental changes at early life stages.”

P 9 line 12: delete “therefore” as seems redundant with “thus”

P 11 line 2: no exposure-response perspective. Reword, “...exposure to increasing perchlorate will have...” or “...exposure to perchlorate can have...”

P 11 line 19: no exposure-response perspective. Reword, “...to perchlorate may also receive...”

P 11 line 22: add “in addition to drinking water” to end of sentence.

P 11 line 30: “Moreover, an acute exposure to perchlorate may be more harmful in the fetus/infant than in the adult.” I agree with this statement, but the preceding text did not provide a basis for this statement (e.g., developmental changes may be permanent changes in phenotype or physiology).

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P 12 lines 12 – 15: Can website or points of contact be provided to insure EPA can reach these efforts if they choose to?

P 12 lines 21 – 22: Given the sampling strategies of NHANES (e.g., different locations as they go through the year oversampling for specific population groups), is likely that one can get statistically valid information from measures of outcome in these people?

P 13 line 6: Add “as described in previous sections.” After “early life stages”.

P 14 lines 3-4: Add “which was used for model calibration” to the end of the sentence on RAIU.

P 14 line6: Make sensitive sub-population” plural.

P 21 line s 34-35: Help clarify sentence and intent by specifically noting example of strong literature on iodide deficiency, hormone changes, and developmental effects.

P 22 line 32: Insert “by” before “clinical evidence”

P 24 Figure 2 box 2: the current model could not address “ downstream hypothyroxinemia”. As noted in the options described at the beginning of these comments, incorporating thyroid hormones would be a highly valuable step, but do we mean to imply here that that is the recommended option? I suggest deleting “and downstream hypothyroxinemia” as the next box addresses going from IUI to thyroid hormone levels and then neurodevelopment.

P 24 Figure 2 box 3c: Is it clear that there is epidemiological data that will linked perchlorate exposure to TH changes? The epidemiological section 3.3 did not seem to indicate that. I suggest deleting from box as there is text discussing some possibilities around this issue.

P 24 line 14: This section appears to need rewording. It seems to indicate that there is data EPA should be using linking perchlorate with neurodevelopmental outcomes, which did not appear to be the conclusion of earlier sections.

P 26 line 11-13: It appears to references have been combined and need to be separated.

REFERENCE

Silva JE, Silva S. Interrelationships among serum thyroxine, triiodothyronine, reverse triiodothyronine, and thyroid-stimulating hormone in iodine-deficient pregnant women and their offspring: effects of iodine supplementation. *J Clin Endocrinol Metab.* 1981 Apr;52(4):671-7

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Dr. Mary A Fox

Section 3.3.3, page 20, line 31

I was not familiar with the terminology of confounding, i.e., “colliders”. There is an article by Sander Greenland that could be cited here for background, if necessary:

Greenland S. 2003. Quantifying Biases in Causal Models: Classical Confounding vs Collider-Stratification Bias. *Epidemiology* 14(3):300 –306.

Section 3.4.1, page 21, line 25

MCLG – letters are out of order

Section 3.4.1, page 22, lines 35-43

Combine these paragraphs. Place period at end of line 37 and delete lines 38-39.

Section 3.4.1, page 23, line 27

This line should read: “ The SAB recommends that EPA use the MOA-based PBPK...”

Section 3.4.2, page 25, lines 20-24

I think this bullet is confusing - the pieces seem out of order and don't correspond well to the other points made. Consider the following:

- The adverse effect. The SAB recognizes a range of neurodevelopmental impairments in the infant as the “adverse effects” e.g., changes in gene expression of genes involved in brain development and function, neuropsychology, and impaired behavior, learning and memory, among others (Rovet and Willoughby 2010). For the purposes of deriving a MCLG for perchlorate, SAB recommends that EPA focus on measurements relevant to these adverse effects including iodine deficiency and hypothyroxinemia.

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Dr. Heiger-Bernays

Having reviewed the comments submitted by my colleagues on the Panel, I have but one comment of substance. The comment is perhaps more of “forest for the trees,” rather than a comment specific to a piece of text. I do not provide my edits on language here since they have been captured by my diligent colleagues.

The SAB Panel was asked to review a white paper and to provide advice to EPA on how it might consider and use recent information and data on life stages, population studies, and PBPK modeling efforts in the derivation of an MCLG as it (EPA) races to complete its analysis and derivation in a very short time-frame. The Panel was asked to focus on the science and not the practicality of balancing the need for convenience with the need for more or innovative analyses.

I suggest that we are struggling with a few recommendations that straddle the “known” and the “less well known” (extrapolated from the literature or from literature that is not directly from the perchlorate human experience) and that the report, as written, in places confuses these two. These are specifically those that relate to our understanding of the epidemiology of perchlorate exposure outcome. In addition, the limits of the PBPK modeling should be more clearly defined. By clarifying the known and inferred in the text and in Figure 2 (page 24), the uncertainties can be better identified. This might allow EPA to focus on those recommendations that are consistent with the data and the objective of the MCLG and to put on its research agenda those recommendations that are important, but cannot possibly be addressed in the next few months. It will also allow a more discrete, well-defined list of recommendations to be presented in the Letter to the Administrator.

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Dr. Julie B. Herbstman

Page 3, line 21: the term “correlates” has a specific biostatistical/epidemiological meaning that I think is beyond what is being implied. Could we change it to “associates” or “relates”?

Page 6, line 6: address should be addresses?

Page 7, line 43: maybe add a clause to this sentence that clarifies that in addition to perchlorate resulting in less iodide for TH biosynthesis (in the mother), it also results in less iodide available for transport to the fetus and breast-fed infant via the placental and breast NIS, respectively, resulting in less iodide for TH biosynthesis in the fetus and infant.

Page 8, line 5: replace correlating with associating?

Page 8, line 15-17: is there any evidence about perchlorate exposure per pound body weight?

Page 11, line 27: reference the appendix where we have discussed the methodological and statistical problems.

Page 12, lines 8 and 10: replace correlating

Page 12, line 21: I think that if we are going to suggest that outcome measures be added to NHANES, we have to mention that the inferences from this will be limited because NHANES is a cross-sectional design. Because of this design, outcome measures would be available only in association with concurrent measures of perchlorate, which may/may not be relevant.

Page 14, line 21/22: the integration section (page 22, line 1-2) defines hypothyroxinemia a little differently; should probably agree on one definition to use throughout.

Page 16, line 16: most studies of perchlorate in humans use urine as the matrix in which to measure perchlorate. Can it be measured in plasma, assuming this is the more meaningful measure? Are there studies that have done this and/or is there a way to infer/model perchlorate concentrations measured in plasma from urine measurements?

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Dr. Judy LaKind

Cover letter/Executive summary

I believe that the Panel is making the following major statements (but I not sure about whether point 4 is correct):

- i. The subpopulation which should be the focus of the MCLG is the hypothyroxinemic pregnant woman.
- ii. This is not the subpopulation currently “protected” by the current RfD, which focuses on women with hypothyroidism.
- iii. Rather than developing a new RfD, the Panel is recommending the use of a PBPK model with which to relate drinking water perchlorate levels with % IUI.
- iv. In order to ensure that the %IUI derived from the model will prevent perturbations in thyroid hormone levels resulting in hypothyroxinemia, the current model needs to be expanded using the current literature on IUI and thyroid hormone levels. Alternatively, the model output giving % IUI can be associated with % perturbation of thyroid hormone levels using available clinical literature.

Assuming these points are correct, I think they need to be made more clearly in the letter, the summary and the document.

Line 15 of pg 2 of the cover letter: I disagree that the proposed approach is more facile and transparent. It may be more rigorous – assuming the model results comport with human data – but for those who are not modelers, this approach feels less transparent and more like a black box than the RfD approach. It is also only more facile for modelers, in my view. Others will not be able to reproduce the results.

Line 24 of pg 2 of cover letter and modeling section: I am not clear on what the short versus long-term goals are with the model. Are there enough human data to model specific thyroid hormone perturbations that correspond to the modeled %IUI? If so, can the modelers/life stage groups provide data for this? For example:

Perchlorate dose (combined perchlorate concentration and drinking water intake)	Modeled %IUI	Δ fT4	Δ TSH

If not, is this something that could be accomplished in the timeframe needed by EPA for its MCLG development?

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Pg 2, lines 7-8: I am not sure what is meant by “important aspects of vulnerability”. Isn’t the panel defining the vulnerable subpopulation already?

Pg 2, line 36: What biological changes? I thought the model currently gave %IUI and that the next step – linkage to thyroid hormone perturbations – was in development. If so, we should be clear here about the limitations and what level of effort (i.e., time) is needed to incorporate thyroid hormone changes into the model.

Pg 6, line 20: Again, I would argue that while a large degree of uncertainty exists in the current approach, it is transparent.

Pg 8, line 3: needs citations

Pg 8, line 20: in the absence of data, I think the wording “likely identical” is too strong. How about “similar”?

Pg 8, lines 10-11: Does this recommendation contradict the earlier statement in the executive summary: “The evidence suggests that the most sensitive life stages for the potential permanent adverse effects of perchlorate on brain development are the hypothyroxinemic pregnant woman and, specifically, her fetus and infants.”

Pg 8, lines 35-38: Can the model do this?

Pg 9, lines 30-31: In my view, the paragraph should start with this sentence.

Pg 10, lines 2-4: Are we really recommending that the expanded model incorporate the short half-life and lower reserves in its code? Or does this consideration happen outside of the model?

Pg 11, lines 16-17: Shouldn’t there be some indication of what kind of *dose* of perchlorate could produce fetal hypothyroxinemia? Or is the group saying that *any* dose could produce this effect?

Pg 11, lines 25-26: It would be useful to have some references here that show the inconsistencies. In general, without supporting citations, I think this paragraph feels more speculative than I suspect the authors mean it to be.

Pg 12, top: Doesn’t this subsection belong with the epi material? For the recommendation that NHANES include child developmental and behavioral questionnaires, I think it would be worth inquiring as to whether this would even be possible (Is CDC willing/able to add more layers to its current lengthy questionnaires?).

Pg 13, lines 8-9: Except that we are suggesting that this may not be a good enough surrogate and that we should be able to link % IUI to changes in thyroid hormone levels, are we not?

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Pg 14, lines 7-9: This could use some expanding. What differences in sensitivity were found across subpopulations? Have these model predictions been shown to correspond with human data?

Pg 14, middle paragraph: I am not clear as to whether the models exist now. The beginning of the paragraph describes “future” models but the remainder of the paragraph suggests that the model exists at present.

Modeling, general: If the currently available model predicts serum thyroid levels based on % IUI, but there are no human data yet to demonstrate validity of model results, are we still recommending that the model – inclusive of thyroid hormone changes - be used to support the current MCLG effort? Since this would be a major change in process for EPA, how much confidence in results is required before moving in this direction?

Pg 19, top: Shouldn't we comment on both sample size and longitudinal variability when describing the results of studies on infant exposure, especially since at the beginning of the section we note that there are studies that can be used to identify highly exposed subgroups?

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Dr. Jennifer Peck

P 6 Line 14: The term “risk” should be replaced with “prevalence” of perchlorate exposure. The studies reviewed do not provide information on the incidence (i.e., new occurrence) of exposure so referring to the reported exposure patterns as “risk” would not be accurate. Prevalence would be the appropriate term to describe the patterns of exposure frequency described in the referenced studies, which assess the proportion of the population defined as exposed at a selected point or period of time.

p.6 Line 18: The traditional algebraic approach for the MCLG is referred to here and in other sections, but not defined in the document. In order to round out the background information that is provided, it would be useful for the MCLG formula to be defined and described in detail somewhere in the report, perhaps within section 3.2 when contrasting the traditional MCLG calculation with the proposed PBPK/PD modeling approach.

p. 6 Line 22: The description of PBPK/PD modeling as “much better from a scientific standpoint” is somewhat vague. It would be helpful to be more specific about the general advantages, if they could be succinctly inserted into this summary section.

p. 8 Section 3.1.2: Although it is addressed in the White Paper, it would seem reasonable for this section to incorporate the key point that “In general, infants (breast-fed and bottle-fed) and children are more susceptible to contaminant exposures than adults because their food consumption and drinking water intake per body weight are greater compared to adults (U.S. EPA, 2009b,c; U.S. EPA, 2011b).” (White Paper, p. 10)

p.8 Lines 21-23: Can we conclude that perchlorate exposure in fetuses, neonate and young children is different from non-pregnant/non-lactating adults due to NIS expression in different tissues (through NIS-mediated transport, specifically in the placenta and lactating breast)? Or, is it the effects of perchlorate exposure (inhibition of iodine uptake and alteration of TH production) that actually differ, or both?

p. 9 Section 3.1.3: Should this section conclude with a recommendation summarizing how the EPA should consider these life stage differences in potential adverse effects when deriving the MCLG? It appears to be the only section without an explicit recommendation.

p.11 Recommendations: In addition to recommendations for future studies, this recommendation section could indicate/reiterate that the EPA can justify the need for a life stage approach to deriving an MCLG given evidence of the susceptibility of the fetus to TH and iodide deficiency during the intrauterine period.

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p.12 Lines 22-23: We may want to consider whether it is reasonable to prescribe that ALL studies of early TH levels should include perchlorate and iodide measurements. Instead, it would seem reasonable to advise that such studies “would benefit from” including such measures.

p.15 Line 36: It may be useful to list a couple of examples to illustrate what it meant by extension of the model to a full population description.

p. 16 Lines 5-7: Should this issue concerning the availability of data on water and diet consumption at different life stages be discussed in more detail in Section 3.1.2 Life Stage Specific Differences in Body Weight and Intakes?

p. 20 Recommendations: Since the recommendations concerning the epidemiology and biomonitoring studies primarily address recommendations for future research, we could consider separating this section into 2 parts, with a paragraph that indicates how the EPA can use the existing data and a paragraph that addresses future studies (similar to how this was handled in section 3.1)

p.20 Lines 30-31 Our epidemiology group may want to revise this statement about confounders, intermediates and colliders to provide a clearer explanation for the general audience.

p.25 Lines 10-11 Since section 3.3.3 acknowledges that caution is needed to consider potential sources of heterogeneity in pooled analyses but does not offer specific guidance for statistical approaches, I would recommend deleting this sentence.

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Dr. Cheryl R. Stein

Overall Comments

Hypothyroxinemia and clinical hypothyroidism need to be defined in the initial discussion of thyroid function in the Life Stage section. Currently these conditions are first defined on page 14 line 21.

The role of thyroid antibodies in thyroid function should be presented in the Life Stage section. Currently thyroid antibodies are primarily discussed in the Epidemiology section, but there is no information about what “presence of thyroid antibodies” means or how this condition may affect thyroid function.

Other competing anions (nitrate, thiocyanate) are only briefly mentioned – first on page 14 line 28. Should the competing role of these other compounds be mentioned sooner and in more detail?

The relative source contribution of perchlorate in drinking water is only minimally discussed. The Charge lists the drinking water RSC for pregnant women as 62%, but based on the literature the RSC for adults may be as low as 20%. The RSC also varies by life stage. Is a discussion of the RSC range not relevant to responding to the Charge questions?

The fact that there is no evidence directly linking perchlorate exposure to thyroid function to adverse health outcomes in humans is not universally apparent throughout the full draft. Perhaps this should be stated in the Executive Summary (page 2 paragraph 1).

I don't understand the recommendation (in the Letter and in Section 3) to look more towards the animal literature. Isn't it more informative at this point to be looking to the human literature?

Specific Comments

Page 1 line 35: “in addition to the data and information used by the NRC” The White Paper did not include the epidemiological studies used in the NRC report. Also on page 5 line 6.

Page 2 line 9: “inhibition of IODIDE uptake” (not thyroid uptake)

Page 2 line 22: What is meant by “acute exposure”?

Page 2 line 23: There are no data on ANY term adverse neurodevelopmental effects of perchlorate – not just long-term effects

Page 2 line 41: Specify “early” and “subsequent” events

Page 3 line 7: “as well as other goitrogens WITH A COMPABABLE MOA”

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Page 3 line 29: “regardless of the cause of those perturbations” So from a health effects standpoint it doesn’t make a difference if the thyroid is affected through the NIS or a different mechanism?

Page 7 line 18: “resulting T3 and more abundant T4” – unclear language about “more abundant”.

Page 7 line 21: “A deficit of TH (during gestation? early childhood? both?) leads to poor brain development. . .”

Page 7 line 32: This section says NIS expressed in stomach, later section (page 13 line 23) says small intestine. Need a consistent list throughout document of tissues with NIS expression.

Page 7 line 42: “levels of T3 and T4 that are ultimately needed by the developing brain.” Are you talking about T3/T4 levels in the pregnant woman? In the fetus? In the neonate?

Page 8 line: Why is measuring organ weight important? This recommendation does not follow from the presented information.

Page 9 line 40: What are the various methodological limitations of the Greer study? Either provide examples or direct the reader to another document describing the limitations.

Page 10 line 4: What are “appropriate” experimental designs?

Page 10 line 12: Define hypothyroxinemia.

Page 10 line 14: Need citation for hypothyroxinemia causing preterm birth.

Page 10 line 28: Define clinical and subclinical hypothyroidism.

Page 11 paragraph 1: Clarify that this is a theoretical model of perchlorate’s MOA and that biologically active dose may differ across sub-pops. Because there is no direct human literature showing this cascade of events, correct?

Page 11 line 18: “through water added to formula preparations” Biomonitoring studies show that there is perchlorate in the formula itself and the amount varies based on type of formula, so there’s probably more in the formula than just what is added with water.

Page 11 line 30: What is meant by “acute exposure”?

Page 11 line 37: Future studies should also measure nitrate, thiocyanate, and thyroid antibodies.

Page 11 line 39: Why should future studies measure heart rate, fetal growth, movement, etc? This recommendation does not follow from anything presented previously. The comment to examine fetal neuroimaging in relation to perchlorate exposure seems out of place and far reaching.

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Page 12 line 8: Be more specific about “later” and “child” outcomes, such as cognition, behavior, growth, etc. Also, it’s not “correlating” perchlorate and outcomes, but rather examining the association between an exposure and an outcome.

Page 12 line 17: “Studies examining child outcome following measurement of perchlorate in breast milk. . .” This should be a separate recommendation – not under Children’s Center.

Page 12 line 22: NHANES already collects some child behavior data. Expanding the child behavior data collected in NHANES is not a particularly useful recommendation because it’s still just a cross-sectional study.

Page 12 line 23: Perchlorate is measured in urine, not blood.

Page 14 line 13: Is Lumen 2012 a human or animal study?

Page 15 line 5: Does the PBPK/PD-IUI model incorporate non-water exposure sources?

Page 15 line 21: Clarify that the “two analyses” refer to two applications of a PBPK model, with one using fixed doses and one using fixed drinking water exposure.

Page 16 line 10: Specify what is meant by “the second analysis”.

Page 16 line 11: What is meant by “perspective on the protection offered by different concentrations”?

Page 17 line 32: How do thyroid antibodies interfere with TH synthesis? What do they mean for thyroid function?

Page 17 line 34: In the total US population 11 – 13% of people have detectable thyroid antibodies. Presumably the prevalence would be higher among the group with thyroid disease and lower among the group without thyroid disease. So how can the prevalence in the healthy subset be 18%? Are these estimates coming from different studies? Needs to be clarified.

Page 18 line 24: Is there a reason to think that the RSC would be different among pregnant women?

Page 19 line 34: Add the range of estimated RSCs.

Page 20 line 33: Briefly state how these model misspecifications may affect interpretation of study results.