

**Comments from Members of the SAB Perchlorate Advisory Panel on the
draft (11/9/2012) report, Advice on Approaches to Derive a
Maximum Contaminant Level Goal for Perchlorate**

(As of November 30, 2012)

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Dr. Hugh A. Barton

- Section 3.1.1 define THs as the abbreviation for thyroid hormones, but this is not consistent through the document. I'd suggest we minimize abbreviations and spell out thyroid hormones. However, for specific hormone such as TSH, T3, T4 etc., abbreviations are appropriate and more readable than the full names.
- P 2 lines 23-25: Looks like cut/paste error. Delete 2nd comma line 24 and fix spelling of "minimally"
- P 9 line 41-43: Add to the end of the first sentence of this paragraph "in a concentration dependent manner"
- P 11 line 7: Make "weight" plural to match "volumes"
- P 14 line 7: The Axelstad et al. reference is not describing effects of perchlorate exposure, but rather the impacts of transient hypothyroxinemia induced by propylthiouracil. Is this cited as well as an example of animal studies demonstrating neurodevelopmental impacts of reduced thyroid hormone levels or does this sentence need to be changed? Change reference to Dilbert and Sui 2008?
- P 17 1st paragraph: To clarify that this entire paragraph is about expanding the model, we could reword the second sentence. "An expanded model would also need to describe dietary iodide intake that is the source of iodide for synthesis of the thyroid hormones, as the current model does not include this."
- P 26 lines 12-13: The sentence does not read correctly. Is it supposed to be "MCLG

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Page 14 Line 36 iodide not iodine

Page 16 Line 11-17 Insertions in bold note deletions with strikeout

PBPK/PD-IUI models described the uptake, distribution and urinary elimination of both perchlorate and radiotracer iodide anions. Serum levels of perchlorate and radiotracer iodide are predicted to describe active transport of perchlorate and radiotracer iodide into cells ~~containing~~ **expressing** the NIS protein, such as the thyroid gland, small intestine, placenta, and **lactating** mammary tissue (Merrill et al. 2005). Both anions, perchlorate and iodide, compete for active uptake by NIS- **expressing** ~~containing~~-tissues. The inhibition of thyroidal uptake of radiotracer iodide by perchlorate is recognized as the primary mode of action for perchlorate leading to potential disruption of the hypothalamic-pituitary-thyroid (HPT) axis by depleting the thyroid gland of iodide used in synthesizing thyroid hormones.

Page 17 Line 25 Strike “of”

Page 18 Line 38 “life stage –dependent”, not “life –stage dependent”

Page 19 Line 5 “life stage –dependent”, not “life –stage dependent”

Page 19 Line 37 the NRC 2005 report are

Page 23 Line 31 exposure categories

Page 26 Line 13 strike a “the”

Line 24 Strike “if”

Page 30 Line 5 Iodine to iodide

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Dr. Claude Emond

- Page 2 line 15 The NRC in 2005 concluded that the first “significant” adverse ...I think we should add the word significant
- Page 10 line 14: We should precise this is a human adult. I do not think this is trivial
- Page 11 line 31: We should talk about drinking water scenarios not (rates), I believe.
- Page 11 line 28-39 We should add a sentence saying “ However, we recognize this effort will take few years before to be incorporated.”
- Page 12 lines 26-28 I disagree with this sentence because the PBPK model is higher sophisticated than the regular approach based on the uncertainty factor. Even at this step the model is correlated with a mode of action.
- “The limitation of the model in its current state, similar to the limitations of the standard MCLG approach, is that the current model describes a precursor event and does not explicitly predict subsequent events or adverse outcomes”.
- I think both approaches are very different, one based on the uncertainty factor (standard approach) and the other (PBPK) based on the biology and the mode of action. For me this is 2 different things. At least in this paragraph it should state what the standard MCLG approach is based on.
- Page 15 line 8-11 The RSC is the relative source of contribution.
- RSC* is the relative source contribution. The RSC is derived as the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (e.g., food) have been considered. The EPA is relying on a total Diet Study developed by the Food and Drug Administration (FDA) for perchlorate. (U.S. EPA 2012)
- This is true but in reality the variation of RSC is between 0 to 1 so it is more an fraction or 20 percent/100 = for example 0.2. So we should change the word percentage by fraction.
- Page 20 lines 2-16, I cannot see what is the recommendation. We should consider to rephrase as a recommendation

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Dr. Jeffery Fisher

Page 15, line 7 Axelstad et al. 2008 is a study with PTU, sentence says perchlorate, double check if ok

Page 17, line 9 replace 'pregnant dam and fetus' with 'pregnant mother and fetus'

Page 3, line 32-33. I am a bit tentative about the statement 'an effort will require...time, in the order of one to several years. Table one (page 29 says 1-2 years), which is more likely. I think they can conduct technical evaluations of the pregnant mom fetus within 3-4 months, and extend the modeling to include newborn and child within a year. I would say this is a one year project for conducting the simulation work, which covers the most sensitive developmental time periods. The Office of Water review process across groups such NCEA, etc. can take time.

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Dr. Mary A Fox

For consistency across sections:

Page 29, lines 8-10, the sentence on model specification. Replace current text with:
'In the recommendations under Section 3.3.3, improved statistical methods are described that
would be relevant for a pooled analysis, if conducted.'

Page 30, lines 3-14 – Check with Lifestage Group that this text is consistent with Section 3.1

For further clarity:

Page 29, Table 1: If needed for clarity, we can add text to Table 1 linking the first 2 potential
next steps to Figure 2.

Typos:

Listing of panel member names: Insert period after middle initial for Mary A. Fox

Page 2, lines 24-25: Extra comma, “minimally”, check spacing

Page 3, line 10: Delete ‘may be’

Page 3, line 29: Replace ‘of’ with ‘or’

Page 18, line 36: Delete ‘An approach of a’, begin sentence with ‘Sensitivity analyses...’

Page 22, line 2: Check units on RfD

Page 25, line 2: Insert ‘of’ after ‘A summary’

Page 25, line 20: Delete comma and extra space

Page 26, line 24: Delete ‘if’

Page 26, line 37: Delete ‘in the figure’ at end of sentence

Page 29, line 27: Delete ‘define:’

Page C-1, line 34: Delete ‘below’ or Replace with ‘above’

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Dr. Heiger-Bernays

After review of the Letter to the Administrator, and the Draft Advisory Report, most of my comments pertain to word use and clarity of the documents. I remain confused, as to exactly who is or are the sensitive populations. I think that we agree that there are sensitive life-stages and this is what was asked in the charge. These are the fetus, the neonate and the infant-child under 2yrs. While I understand that this topic has been discussed at length, we need to clarify our terms so that the document is internally consistent. Can we clearly identify who is in need of protection from the effects of perchlorate, or recommend to EPA that this is something that needs to be identified?

General comment on both the letter and the document: watch the use of the words “vulnerable” and “sensitive” “susceptible” - [I think that the sensitivity refers to biological differences that make an individual or group more susceptible to the effects and vulnerability refers, at least in part, to the behavior that increases exposure]

Letter to Administrator

- P1 Line 18: chlorine-based disinfection products
- Line 20: ~~an~~ adverse health effects
- Line 23: titled or entitled: *Health Implications of Perchlorate Ingestion*
- Line 28: following “iodine uptake” add “into the thyroid”
- Line 29: ...Reference Dose (RfD)
- Line 30: change no observed effect level of 7 µg/kg/day to No Observed Effect Level of 7 µg/kg-day
- Line 31: following ...inhibition ... add “into the thyroid”
- Line 32: change... the healthy adults and the.... tothe healthy adults in the study and the
- Page 2.
- Line 14: insert “of effects or adverse effect” between “their” and “risk”
- Line 24: insert “data-driven” between “more” and “rigorous”

Document

- List of participants: Line 30: revise to read: Dr. Wendy Heiger-Bernays, Associate Professor of Environmental Health, Boston University School of Public Health, Boston, MA
- Pg 1; line 24-25. correct spacing
- Pg 2: line 5: include infants since these are called out previously as sensitive populations

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- Pg 8 line 13. PBPK models can be used for estimating exposure/absorbed dose, dose at target, but isn't it the PD portion that models the impacts?
- Pg 10 lines 8-16: several terms are used here, probably because of the use by the authors of the citations, but we need to be consistent with terminology throughout the document: hypothyroxinemia and subclinical hypothyroidism – are they the same? Not to make more work, but is there a place or a need for definitions?
- Pg 10 line 40: since this section addresses body weight, metabolism and not effects, should reference to pharmacodynamics be included?
- Pg 12: line 17: refers to “the other two areas”, but I think line 15 refers to three others in addition to perchlorate on brain development. Can this be clarified?
- Pg 12-13 Section 3.1.3 refers to conclusions from rodent studies. Might it be important to include a statement about how the thyroid-brain axis in mice? Rats? compares with that of the human?
- Pg 12: line 32: ...perchlorate effects will be observed in breast milk once the infant starts to feed... does this refer to TH or to I?
- Pg 13. Line 27. Refers to hypothyroxinemia and subclinical hypothyroidism as different entities.
- Pg 14. Line 32: are there epi data that show that the fetus and infant is more sensitive to the effects of perchlorate? If so, please cite.
- Pg 16: line 14: refers to NIS-containing tissues – are these the same that are described in section 3.1.2?
- Pg 21, lines 15
and 21: These metrics refer to exposure estimates.
- Pg 22: line 3. Might this be reworded to perchlorate “dose”, rather than “reference dose”? The intention is that some portion of the Reference Dose (the RSC) is allocated to consumption of water and the remainder to other exposures.
- Pg 24: lines 4-6: Is the recommendation to determine the validity or accuracy of a spot urine value with alternative urinary measure? Can this be clarified?
- Pg 25: Line 5: ...of the SAB was is that..
- Remainder of Section: review for sensitive subpopulations/lifestages so that document clearly states who these are and that they are consistent throughout the document.

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Dr. Julie B. Herbstman

I think we need to define hypothyroxinemic up front—it seems to be defined slightly differently in each section (although the meaning is similar)--see examples:

- Page 13, line 8: hypothyroxinemia (i.e., low TH levels)
- Page 17, line 18: hypothyroxinemia (decrease in serum T4 and no change in serum TSH)
- Page 25, line 6: hypothyroxinemia (defined as “fT4 levels below the 10th percentile and concomitant TSH values $<2.0 \mu\text{mU/L}$ ”)

Page 13, line 35: “. . .impaired development of the brain and suboptimal outcome”: what is the suboptimal outcome? Maybe ‘suboptimal neurodevelopment’ instead of outcome?

Page 14, line 22: sentence ending in “. . .supply due to perchlorate” needs a reference, I think.

Page 14, line 31: replace “(see epidemiology section)” with “Section 3.3.2”.

Page 19: epidemiology section: maybe we should replace “subgroups” with “subpopulations” throughout this section to be consistent with footnote #1 on page 6 that defines the term “subpopulation” (which I think is really what we mean when we say “subgroup”).

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Dr. Judy LaKind

- P 5, line 23: "healthY"
- P 10, lines 11-13: I believe that earlier in the document, hypothyroxinemia was defined as subclinical hypothyroidism. Here they are described as separate entities. We should be consistent.
- P 10, lines 18-22: This doesn't read right. Do you mean "despite" instead of "due to"?
- P 14, lines 31-33: We note that the epi data are inconsistent and methodologically flawed but then say that the findings show definitively that infants are more susceptible. This seems contradictory. However, if the findings from the epi studies *do* show this, we should provide references.
- P 17, top: Does the model shed light on *sensitivity* of life-stages to RIUI or does it shed light on the *amount* of RIUI for a given life-stage?
- P 17,
first full paragraph: The language is a blended discussion of current and future model capabilities. Can we be clearer about what is available to EPA today and what would be helpful to EPA in the future?
- P 19, line 37: fix grammar
- P 20: I propose that we stick with "iodide" since we are interested on the anion.
- P 21, top paragraph: Does this text imply that EPA should include women who are antibody positive in the list of sensitive subpopulations? They are not currently included in our list.
- P 21, lines 15
and 21: Why are exposure and dose both written here? What is the difference in this context?
- P 21, paragraph
starting on line 39: If we are going to highlight these studies, we should include the N for each one and weigh in on study strengths/weaknesses (even if it just a summary of Appendix B).
- P 23, line 8: While this is defined in Appendix B, it would be good to clarify here what we mean by "misspecified statistical models".
P 23, line 33: It would be useful to have a definition of "directed acyclic graphs" here.
- P 25, lines 2-3: sentence needs help. Remove "a summary"?
- P 29, line 26: remove stray colon
- P B3, line 4: text says 4 studies, but 3 are cited

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Dr. Paul Lipkin

I have primarily reviewed the sections that reflect my group's work and the content area that I understand best. Attached are my (minor) comments on what is an excellent report. There seems to be a lot of redundancy on the life stage issues, but that is a major undertaking to prune it and may not be of any value to the EPA.

Executive Summary

Page 2, lines 24-25: delete second comma; correct wording "minimally iodide".

Section 3 "Response to Charge Questions":

Page 10 lines 37-40: I don't understand this 'in addition' point and how it relates to the sentences before.

Page 11, lines 38- 39: Change into 3 sentences: ...altered thyroid status. However, the changes... upon return to euthyroid status. Therefore changes in thyroidal...."

Page 12, line 3: Suggested rewrite for clarity: "...fourth month of gestation (refs), with earlier fetal brain development being totally reliant on the maternal TH supply."

Page 12, line 37: Suggested rewrite: "When determining safe levels of perchlorate in drinking water, the EPA should consider..."

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Dr. Jennifer Peck

- p. 21 Line 26-27. Is Mendez et al. 2010 the correct reference for the statement that creatinine adjustment is less effective during pregnancy? This information does not appear to be addressed in this paper.
- p. 26 Line 18-19 To be more clear about what is meant by the term “point estimates”, we could add to the last phrase... “rather than point estimates representing average population values”.
- p. 29 Line 9 I would recommend adding “potential non-linearity of effects...”
- p. 29 Line 12 I would recommend omitting the last sentence. “A pooled analysis requires substantial effort.” This would not be unique to pooled analyses.
- p. 29 I am concerned this section may be placing too much emphasis on the potential value of pooled analyses as a next step in an integrated approach for deriving an MCLG for perchlorate. A pooled analysis of the Pearce et. al. studies would still require cautious interpretation regarding causal inference because the data are cross sectional.

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Dr. Cheryl R. Stein

General Comments

Overall the report reads very well and appears close to final form. I have only a couple of overall comments, plus some specific suggestions.

(1) The 2nd page of the letter to Administrator Jackson equates hypothyroxinemia with subclinical hypothyroidism (line 17). An actual definition of this condition, however, is not provided until the Integration section, page 24, line 6. Hypothyroxinemia/subclinical hypothyroidism should be explicitly defined at the beginning of the report. Additionally, the equivalence of hypothyroxinemia and subclinical hypothyroidism is not evident in the life stage section.

(2) The Life Stage section is a bit repetitive. Perhaps the repetition could be alleviated by first providing all of the needed biological and clinical background information on iodine, thyroid hormone, and perchlorate. Then each of the sub-sections doesn't need to repeat the background information.

Specific Comments

Page ii, line 7 delete "rate"

Page ii, line 21 "goal" and "level" are inverted

Page ii, line 32 should be "PBPK"

Page ii, line 41 TDS isn't used as an acronym in the text – Total Diet Study is written out

Page 2, line 24-25 delete extra comma at end of line and correct typo at beginning of next line – not sure if it should be "minimally" or "nominally" iodine deficient

Page 3, line 10 delete "are" from "may be useful"

Page 5, line 23 missing a Y for "healthy"

Page 7, line 9 missing ES for "addresses"

Page 8, line 13 capitalize "Agency's"

Page 8, line 17 change to "precluding their APPLICABILITY to deriving the MCLG"

Page 10, line 2 reorder the sentences so that "Clearly a primary downstream effect. . ." is the final sentence in the paragraph

Page 10, line 10 together with line 13, an example where hypothyroxinemia and subclinical hypothyroidism are being presented as different entities. Also if this is the

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first mention in the text the explicit definition from the Integration section could be provided.

- Page 10, line 18 I'm not sure I understand this point. If it's difficult to relate specific molecular brain changes with later outcomes, how can these brain alterations be considered adverse effects?
- Page 11, line 16 "for both anions" – which two anions? It would be clearer to specify which anions are being referenced
- Page 12, line 21 change to "shorter TH half-life"
- Page 12, line 34 Are you comparing pregnant and non-pregnant adults? Only one side of the comparison is stated.
- Page 13, line 27 Another example of differentiating between hypothyroxinemia and subclinical hypothyroidism
- Page 15, line 1 Are you recommending that human fetuses under neuroimaging? This seems a bit extreme.
- Page 19, line 37 change to "since THE NRC report ARE useful"
- Page 21, line 2 add a space after "(2002)"
- Page 21, line 21 add a space after "(2011)"
- Page 22, line 37 delete "n="
- Page 23, line 5 change to "support a DERIVED MCLG"
- Page 26, line 12 change to "on a potential MCLG, the SAB"
- Page 29, line 27 delete "define:"
- Page B-4, line 26 change to "because EVEN hypothyroxinemia"