

**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**

Sorted by Section
(As of December 3, 2012)

General

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? (Heiger Bernays)

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] (Heiger Bernays)

(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. (Stein)

(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. (Stein)

Remainder of Section: review for sensitive subpopulations/lifestages so that document clearly states who these are and that they are consistent throughout the document. (Heiger Bernays)

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

- 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 µmU/L”)

Specific Comments

Letter to the Administrator

- Page 1** Line 17 Strike man-made insert “artificially synthesized” (Carrasco)
- Line 18: chlorine-based disinfection products (Heiger Bernays)
- Line 20: ~~an~~ adverse health effects (Heiger Bernays)
- Line 23: titled or entitled: *Health Implications of Perchlorate Ingestion* (Heiger Bernays)
- Line 24 Insert contamination perchlorate *contamination* could....(Carrasco)
- Line 24: replace “which” with “and this” (Rovet)
- Line 25: Add “It is well established in the scientific literature that” before “Decreased” (Rovet)
- Line 28: following “iodine uptake” add “into the thyroid” (Heiger Bernays)
- Line 28: “be used” after “effect” (Rovet)
- Line 29: ...Reference Dose (RfD) (Heiger Bernays)
- Line 30: change no observed effect level of 7 µg/kg/day to No Observed Effect Level of 7 µg/kg-day (Heiger Bernays)
- Line 31: following...inhibition ... add “into the thyroid” (Heiger Bernays)
- Line 32: change... the healthy adults and the.... tothe healthy adults in the study and the (Heiger Bernays)
- Lines 29-32: sentence is too long, suggest breaking into two (Rovet)
- Line 33: “and” instead of “but” maybe (Rovet)
- Line 34: “the RfD” instead of “it” (Rovet)
- Line 34: Add a link like “Consequently” to start this sentence (Rovet)
- Lines 43-44: You have changed tense – check if best (Rovet)
- Page 2** Line 3: SAB – first time mentioned – perhaps a better introduction to it (Rovet)
- Line 7: “has” before “reviewed” (Rovet)
- Line 7: “thus” before “concludes” (Rovet)
- Line 7: is “that” necessary (Rovet)
- Line 14: add “and the known role of thyroid hormone on human brain development” after “action” (Rovet)
- Line 14: insert “of effects or adverse effect” between “their” and “risk” (Heiger Bernays)

- Line 15 The NRC in 2005 concluded that the first “significant” adverse .I think we should add the word significant (Emond)
- Line 17: subclinical hypothyroidism is not the same as hypothyroxinemia – take out clause on subclinical (Rovet)
- Line 24: insert “data-driven” between “more” and “rigorous” (Heiger Bernays)
- Page ii, Line 7** delete “rate” (Stein)
- Line 21 “goal” and “level” are inverted (Stein)
- Line 32 should be “PBPK” (Stein)
- Line 41 TDS isn’t used as an acronym in the text – Total Diet Study is written out(Stein)

1. Executive Summary

- Page 1** Line 14: We should precise this is a human adult. I do not think this is trivial (Emond)
- Line 24 fix spacing and typos (Carrasco)
- Line 33 iodide not iodine (Carrasco)
- Page 2: Line 5: include infants since these are called out previously as sensitive populations (Heiger Bernays)
- Line 15 The NRC in 2005 concluded that the first “significant” adverse .I think we should add the word significant (Emond)
- Line 18 “but are readily reversible”: found this confusing (Rovet)
- Lines 23-25: Looks like cut/paste error. Delete 2nd comma
- Line 24 and fix spelling of “minimally” (Barton) (Lipkin) (Stein) (Fox)
- Lines 24, 25: ?move “pregnant women” after hyothyroxinemic and then add idea of minimally iodide deficient, if even necessary (Rovet)
- Line 31: We should talk about drinking water scenarios not (rates), I believe. (Emond)
- Line 28-39 We should add a sentence saying “ However, we recognize this effort will take few years before to be incorporated.” (Emond)
- Page 3** Line 10 nonetheless, Maybe or are (Carrasco) (Stein) (Fox)
- Line 10: “Nonetheless (Rovet)
- Line 10: “that the current epidemiology may be useful (Rovet)
- Line 11: colon after” estimate” (Rovet)
- Lines 11- 14: add “(i)” before “the size”, “(ii)” before “the extent” – take out “estimate”, and “iii” before “the relative” and take out “estimate” (Rovet)

Line 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. (Emond)
“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”. (Emond)
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. (Emond)

Page 3, Line 29: Replace ‘of’ with ‘or’ (Fox)

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. (Fisher)

Line 36: should lactating be mentioned? Should offspring be mention” (Rovet)

Line 41: “adverse health effects” does not convey to me the issue of fetal/infant brain development (Rovet)

Page 4 Line 2: change “neurobehavioral” to “neurodevelopmental” (Rovet)

2. Introduction

Page 5 Line 4 Strike man-made insert artificially synthesized (Carrasco)

Line 9-16 Insert bold text. (Carrasco)

In 2005, at the request of EPA and other federal agencies, the National Research Council (NRC) published a comprehensive report *Health Implications of Perchlorate Ingestion* (2005). The NRC concluded that perchlorate can affect thyroid function because it is an ion that competitively inhibits the transport of iodide into the thyroid by a protein known as the sodium /iodide symporter (NIS). Significant inhibition of iodide uptake results in intra-thyroid iodine deficiency, decreased **BIO**synthesis of **THE** key thyroid hormones triiodothyronine (T3), **AND** thyroxine (T4), and increased thyroid stimulating hormone or thyrotropin (TSH). The NRC also concluded that a prolonged decrease of thyroid hormone can have adverse effects in sensitive populations (e.g., people with thyroid disorders, pregnant women, fetuses, and infants).

Line 23: "healthY" (LaKind) (Stein)

Line 25 Strike “the” (Carrasco)

Page 6 Line 8 to 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. (Emond)

Page 7, Line 9 missing ES for “addresses” (Stein)

3. Response to Comments

Page 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? (Heiger Bernays)

Page 8, Line 17 change to “precluding their APPLICABILITY to deriving the MCLG” (Stein)

Line 26: state what “it” is, right now refers to “body” (Rovet)

Line 29: “experienced” to “experience” (Rovet)

3.1 Life Stages

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. (Barton)

Page 9 Line 18 Insert “thyroid” cell(Carrasco)

Line 30 Change earlier to early(Carrasco)

Line 41-43: Add to the end of the first sentence of this paragraph “in a concentration dependent manner” (Barton)

Page 10, Line 2 reorder the sentences so that “Clearly a primary downstream effect. . .” is the final sentence in the paragraph(Stein)

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? (Heiger Bernays)

- Line 10 together with Line 13, an example where hypothyroxinemia and subclinical hypothyroidism are being presented as different entities. Also if this is the first mention in the text the explicit definition from the Integration section could be provided. (Stein)
- 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. (LaKind)
- Lines 18-22: This doesn't read right. Do you mean "despite" instead of "due to"? (LaKind)
- 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? (Stein)
- Lines 20-22: this part doesn't make sense to me (Rovet)
- Line 40: since this section addresses body weight, metabolism and not effects, should reference to pharmacodynamics be included? (Heiger Bernays)
- Lines 37-40: I don't understand this 'in addition' point and how it relates to the sentences before. (Lipkin)
- Page 11** Lines 2 – 16 I cannot see what is the recommendation. We should consider to rephrase as a recommendation (Emond)
- Line 16 "for both anions" – which two anions? It would be clearer to specify which anions are being referenced (Stein)
- Line 7: Make "weight" plural to match "volumes" (Barton)
- Line 7: "flow" not "flows" (Rovet)
- Line 9: add "scientific" before "literature" (Rovet)
- Line 15: whose thyroid gland – mention both mother's and fetus's/child's (Rovet)
- Line 18: move "are" before "adults" (Rovet)
- Line 26: add "where it" before "binds" (Rovet)
- Line 38 Insert "not" however (Carrasco)
- Line 39 Make two sentences statue. Therefore (Carrasco)
- Lines 38 and 39: Change into 3 sentences: ...altered thyroid status. However, the changes... upon return to euthyroid status. Therefore changes in thyroidal...." (Lipkin)
- 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." (Lipkin)
- 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? (Heiger Bernays)

- Lines 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? (Heiger Bernays)
- Line 21 change to “shorter TH half-life” (Stein)
- Line 32: ...perchlorate effects will be observed in breast milk once the infant starts to feed... does this refer to TH or to I? (Heiger Bernays)
- Line 32: “. . .and that perchlorate effects will be observed in breast milk”: I’m not sure what this means—is it that perchlorate will affect iodine transport via breast milk? (Herbstman)
- Line 34 Are you comparing pregnant and non-pregnant adults? Only one side of the comparison is stated. (Stein)
- Line 37: Suggested rewrite: “When determining safe levels of perchlorate in drinking water, the EPA should consider...” (Lipkin)
- Page 13.** Line 27. Refers to hypothyroxinemia and subclinical hypothyroidism as different entities. (Heiger Bernays) (Stein)
- Line 32: not happy with “even the least severe TH inadequacy”; can we tone down? (Rovet)
- Line 38: change “depend on” to “reflect directly (Rovet)
- Page 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? (Barton)
- Line 7 Axelstad et al. 2008 is a study with PTU, sentence says perchlorate, double check if ok (Fisher)
- Line 7: change “reflect” to “reflected” (Rovet)
- Line 22: sentence ending in “. . .supply due to perchlorate” needs a reference (Herbstman).
- Line 31: replace “(see epidemiology section)” with “Section 3.3.2”. (Herbstman)
- 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. (LaKind)
- 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. (Heiger Bernays)
- Line 34: reword “the fully developed adult brain” (Rovet)
- Line 36 iodide not iodine (Carrasco)

Page 15, Line 1 Are you recommending that human fetuses under neuroimaging? This seems a bit extreme. (Stein)

3.2 PBPK Modeling

Page 16: Line 14: refers to NIS-containing tissues – are these the same that are described in section 3.1.2? (Heiger Bernays)

Line 11-17 Insertions in bold (Carrasco)

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. (Carrasco)

Page 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? (LaKind)

first 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? (LaKind)

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.” (Barton)

Line 9 replace ‘pregnant dam and fetus’ with ‘pregnant mother and fetus’ (Fisher)

Line 18: I am not sure about “no change in serum TSH”. It may change but still remain in the normal range. In my experience every time T4 changes, TSH shows an effect (Rovet)

Line 18: take out “for” (Rovet)

Line 25 Strike “of” (Carrasco)

Line 25: move “also” to after “could” (Rovet)

Line 32: can you strengthen “much” (Rovet)

- Line 35: change “as well as” to “and (Rovet)
- Line 37: change “documentation” to “information (Rovet)
- Line 44: add “to” after “finally” (Rovet)
- Page 18**, Line 8: “in the various literatures” (Rovet)
- Line 9: “relationships” (Rovet)
- Line 33-36: this is a very good point and I wonder whether this might be mentioned earlier when the UF approach was discussed; also in this section, I wonder whether you might mention environmental differences in iodine availability (Rovet)
- Line 36: Delete ‘An approach of a’, begin sentence with ‘Sensitivity analyses...(Fox)
- Line 38 “life stage –dependent”, not “life –stage dependent” (Carrasco)
- Lines 40-41: I found this whole sentence far too long to read but perhaps just putting commas around “if they occur,” may work (Rovet)
- Page 19** Line 5 “life stage –dependent”, not “life –stage dependent” (Carrasco)
- Lines 5-7: I found this ending skimpy. Can you elaborate (Rovet)
- Line 10: “at this time” after “MOA” (Rovet)
- Line 10: add “Nevertheless” before “this (Rovet)
- Line 10: change to “this step can be usefully extended” (Rovet)
- Line 15: am not happy about the word “protection”; conveys wrong message (Rovet)
- Lines 18-20: again, this info should be highlighted earlier (Rovet)
- Lines 24-26: sentence is vague (Rovet)

3.3 Epidemiological Studies

- 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”) (Herbstmnan).
- Line 37 change to “since THE NRC report ARE useful” (Stein)
- Line 37 the NRC 2005 report are(Carrasco)
- Line 37: fix grammar (LaKind)
- Page 20:** I propose that we stick with "iodide" since we are interested on the anion. (LaKind)

- Lines 11-12: Please explain. Is it possible the perchlorate can tip the balance from hypothyroxinemia to hypothyroidism? (Rovet)
- Line 30: haven't the WHO guidelines been revised? Might you not cite the Hallowell et al, Thyroid, guidelines here; I was part of the team that went to the WHO and we there established new guidelines from 1994 (Rovet)

Page 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. (LaKind)
- Line 2 add a space after "(2002)" (Stein)
- Line 9: complete thought (Rovet) Line 19: need to stress younger ages not studied (Rovet)
- Line 21 add a space after "(2011)" (Stein)
- Line 15- 21: These metrics refer to exposure estimates. (Heiger Bernays)
- Lines 15- 21: Why are exposure and dose both written here? What is the difference in this context? (LaKind)
- Page 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. (Peck)
- Line 30: complete thought (Rovet)
- Line 39: Change to: "four studies provide useful information" and take out "is...studies" (Rovet)
- Line 39-on 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). (LaKind)
- Page 22, Line 2:** Check units on RfD
- 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. (Heiger Bernays)
- Line 36: space after (2008) (Rovet)
- Line 37 delete "n="(Stein)
- Line 41: should you not mention that milk/water a higher percentage of RSC in neonates and infants than older children? (Rovet)

- Page 23, Line 5** change to "support a DERIVED MCLG" (Stein)

- Line 8: While this is defined in Appendix B, it would be good to clarify here what we mean by "misspecified statistical models". (LaKind)
Page 23 Line 31 exposure categories(Carrasco)
- Line 8: perhaps expand "mispecified statistical models a bit to convey linear approach doesn't specify effects at extremes. I know it comes later but thought when reading this, I needed an explanation (Rovet)
- Line 15: were the pregnant women in NHANES geographically representative of the US population; just wonder, if sample size was restricted (Rovet)
- Line 28: Might you mention specific studies (Rovet)
- Line 33: It would be useful to have a definition of "directed acyclic graphs" here. (LaKind)
- Line 40:** Should you not have mentioned meta-analysis/pooled approach here? (Rovet)
- Page 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? (Heiger Bernays)
- Lines 4-6: Maybe separate exposures to get point across, eg. Perchlorate and iodide versus nitrate and thiocyanate (Rovet)
- Line 40: "adverse health effects: indicate neurodevelopmental outcome (Rovet)
(Rovet)

3.4 Integration of Information

- Page 25,** Lines 2-3: sentence needs help. Remove "a summary"?(LaKind) Insert 'of' after 'A summary' (Fox)
- Line 5: ...of the SAB was is that.. (Heiger Bernays)
- Line 8: TSH values vary by trimester (Rovet)
- Line 11-12: should you not mention lactating mothers (Rovet)
- Lines 11-12: "and how these adverse effects impact on the neurodevelopment" (Rovet)
- Line 12: not quite accurate as we don't know of the neurodevelopment of the fetus, just the potential impact on its brain development (Rovet)
- Line 20: Delete comma and extra space (Fox)
- Page 26** Lines 12-13: The sentence does not read correctly. Is it supposed to be "MCLG of perchlorate" ? (Barton) (Stein)
- Line 13 strike a "the" (Carrasco)

- Lines 12-19: Great point. Should this not be mentioned earlier in the Epidemiology study (Rovet)
- 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”. (Peck)
- Line 24 Strike “if” (Carrasco) (Fox)
- Page 28** Lines 20-22: Lose me here (Rovet)
- Line 34: Is the study by Silva and Silva or Silva and Larsen – can someone check, going from memory; Silva was Larsen’s student at the time (Rovet)
- 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.’ (Fox)
- Line 9 I would recommend adding “potential non-linearity of effects...” (Peck)
- Line 12 I would recommend omitting the last sentence. “A pooled analysis requires substantial effort.” This would not be unique to pooled analyses. (Peck)
- Line 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. (Peck)
- Lines 19-20 Table 1: If needed for clarity, we can add text to Table 1 linking the first 2 potential next steps to Figure 2. (Fox)
- Line 26: remove stray colon(LaKind)
- Line 27 delete “define:” (Stein) (Fox)
- Page 30,** Suggestion: can the bullets be numbered? (Rovet)
- Line 2: take out “Define” (Rovet)
- Line 2: brain is affected earlier while behavioral impact extends far past infancy (Rovet)
- Lines 3-14 Check with Lifestage Group that this text is consistent with Section 3.1 (Fox)
- Line 5 Iodine to iodide (Carrasco)
- Line 16: take out “Define” (Rovet)
- Line 17: shouldn’t you mention the lactating woman (Rovet)

Appendix B

- Page B1**Line 15: change “approximately” to “minimally” (Rovet)

Line 25: change “tested” to “assessed” – a bit broader (Rovet)

Line 30: Why not older? Effects may only be observed in adolescence from an earlier impact on the brain (Rovet)

Page B2, Lines 17-21: Might you not mention drinking bottled water, which can come from regions with higher perchlorate levels and conversely drink good bottled water in regions of high perchlorate levels (Rovet)

Line 26: “grossly inaccurate”: Why? (Rovet)

Lines 28-32: I found these sentences a bit jumbles (Rovet)

Line 30: After (2006). Can you explain a bit better (Rovet)

Line 33: Might you also mention seasonal differences in water consumption (Rovet)

Page B3 Line 4: text says 4 studies, but 3 are cited (LaKind)

Line 14: and so, -- finish sentence (Rovet)

Page B4 Line 26 change to “because EVEN hypothyroxinemia” (Stein)

Line 27: Is this the best article? Isn’t it on hypothyroxinemia of prematurity? Please check. (Rovet)

Page B6 Line 35: comma after “models” (Rovet)

Page B7 Line 2: comma after “T3” (Rovet)

Appendix C

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