Preliminary Comments from Members of the Chartered SAB on the SAB Draft Report *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate*

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Comments from lead reviewers

Comments from Dr. Edward Carney

1. Were the charge questions adequately addressed?

General comments

Due to the absence of human data causally linking early life stage exposure to perchlorate (PC) exposure to neurobehavioral effects and the obvious difficulties in getting such data in the future, EPA has been exploring a new risk assessment approach based on mode of action and physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling. This type of approach is clearly where toxicology and risk assessment science are heading, and the approach was appropriately endorsed by the SAB. The SAB also pointed out the limitations of the approach as it currently stands, and made a number of excellent suggestions for further research and improvement. While in general, the charge questions were adequately addressed, some comments on a few specific charge questions are warranted:

Life stages

The report devotes a significant amount of general discussion to the importance of thyroid hormone on neurodevelopment to justify addition of infants as a "sensitive life stage" (NRC already had included fetuses as such). Apparently there are few if any data directly addressing the effects of PC exposure during infancy, so the inclusion of infants as a sensitive life stage is based on inference of potential effects. Nonetheless, based on the underlying knowledge of basic biology, it is reasonable to consider infants as a sensitive subpopulation.

Understanding the degree to which fetuses vs infants are sensitive to PC-induced effects depends on knowledge of life stage-specific pharmacokinetic and pharmacodynamic factors. As the current model only goes up to the initiating precursor event (IUI), use of the model in its current form is likely to be inaccurate (overly conservative). What appears to be lacking is an understanding of the amount of IUI needed to induce hypothyroxinemia – is it 25%, 50% 75%, etc? Therefore, the SAB appropriately emphasized the need for more data on downstream events, particularly data on the hypothalamic-pituitary-thyroid axis and stage-specific differences in its ability to compensate for changes in iodide status. A minor suggestion to make the report more useful to EPA would be to delineate the specific types of data needed to inform the fetal life stage assessment vs. the neonatal/infant life stage assessment. Many sections in the current report tend to lump together fetal and infant sensitivity, even though the factors which drive these sensitivities are quite different.

PBPK/PD Modeling Approach

Again, the SAB expressed support for a PBPK/PD modeling approach. However, the current model only covers the initial step in the mode of action (i.e., inhibition of iodide uptake), which is necessary, but not sufficient, for the induction of adverse effects. SAB encouraged EPA to "expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from PC exposure". This recommendation is quite appropriate and important, as the latter effects represent the appropriate point of departure in the risk assessment (as opposed to the precursor event). The SAB also went further by

recommending an interim approach which uses the existing PBPK/PD model based on IUI, and then extrapolates to an appropriate point of departure (i.e, thyroid perturbation) based on "empirical observations" from the clinical literature. These empirical observations would identify the degree of IUI needed to induce a measurable, clinically significant hypothyroxinemia.

While this concept makes sense in that it offers a route back to an appropriate point of departure, it is unclear whether these empirical clinical data already exist in the literature. If they do exist, they should be cited and discussed more prominently in the report. This would offer much needed perspective, especially as the current RfD is based on a mere 1.8% inhibition of iodide uptake. In contrast, some of the public comments mention that far greater inhibition of uptake is needed to induce hypothyroxinemia. If on the other hand, these data are not already available, then the one year time frame to institute the interim approach would seem overly optimistic.

<u>Integration of information</u>

From a technical perspective, the SAB report seems to have adequately addressed the first charge question related to using the total body of information to derive the MCLG. However, the report appeared to fall short in addressing the second charge question:

"*How can EPA use the available data to estimate reductions in adverse health effects (i.e., dose response) that are likely to result from reducing perchlorate levels in drinking water?"*

This question is of critical importance as it bridges the science to policy, specifically informing EPA as it considers risk management options and opportunity costs associated with alternative public health activities.

In this context, it would seem that if we know enough about PC's mode of action to support a risk assessment, then we should also be able to make at least a rough estimate of the reduction in adverse health effects likely to be realized by reducing PC levels in drinking water. This concept is minimally addressed in the last sentence of the report, which states:

"EPA may be able to begin to estimate reduction in adverse health effects from reducing perchlorate levels in drinking water by examining shifts in the distribution of exposure to the sensitive subpopulation if relevant data are available."

Perhaps another way to think about this would be to theoretically compare the normal distribution of iodide status that reflects both iodine intake and intake of PC in the US population and then estimate the degree to which the distribution would shift under the possible standards. It would be particularly useful to estimate the number of people who would be expected to shift from iodide insufficient to iodide sufficient status and the incremental impact on those who are iodide insufficient.

Similarly, knowledge of mode of action suggests there would be great value in incorporating PC in a cumulative risk assessment which considers the impact of other goitrogens to which humans are commonly exposed. This also would be of great benefit to the agency as it determines the most effective and efficient means of deriving the desired health benefit.

Based on the above, it is strongly recommended that the report draw more information from the body of the report to provide EPA with some sense of the expected health benefit of reducing PC levels in drinking water, and also that they weigh in on the value of considering cumulative risk.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

There were no glaring errors or omissions of which I am aware. However, the report tended to describe the biology and toxicology in qualitative terms, and often did not provide a dose-response context for much of the information provided. It is suggested that the dose levels associated with key events be included whenever possible.

3. Is the draft report clear and logical?

The report was generally clear and logical, although the use of the term “PBPK” was not always used appropriately. Often “PBPK” was used in a discussion of pharmacodynamics. It is suggested that “PBPK/PD” be used consistently to avoid any confusion.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

In general - yes. The only suggestion regarding the conclusions is that they should be more explicit with respect to readiness (or lack thereof) of the current model. The report mentions limitations of the current approach and offers three options for advancing. This would imply that the current model is not recommended for use at this time, but it would be helpful to be explicit on this matter.

Comments from Dr. Elaine Faustman

1) Were the charge questions to the committee adequately addressed?

The SAB provided a detailed report that addressed the Charge questions on Perchlorate relating to use of Sensitive Life Stages, PBPK, Epidemiology Evidence and Integration of Information. In general the SAB panel supported both approaches by the NRC report and EPA's approaches but asked EPA to move forward to apply a more fully developed MOA framework for assessment of Perchlorate. The report provided a rich variety of suggestions with a primary emphasis on modeling suggestions.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

In general the report emphasizes more explicitly the importance of integrating information across sectors within a PBPK/PD model modeling approach. This is well supported and documented. The SAB review should further clarify several of the points listed below in item 3.

3) Is the draft report clear and logical?

The report presents the discussion, references used by the panel and summary statements in such a way that the reader can clearly see the final recommendations from each section of the report.

This reviewer would request further clarification of several points:

First, it was unclear to this reader the suggested re- writing and identification of sensitive populations: "Thus the sensitive populations for perchlorate exposure are hypothroxinemic pregnant and lactating women and infants exposed to perchlorate through either water-based formula preparations or breast milk." (Page 10-11, and numerous other places in the document and executive summary, page 2 lines 23 to 27). It was unclear why the in utero fetus was deliberated omitted from this frequently used statement. Please clarify.

Document should clarify whether the use of the word "fetus" when used is used to mean the developing human at greater than 9 weeks. Was the panel convinced that the developing embryo was not at risk during in utero development due to thyroid alterations given their own statements about "early brain development"? Please clarify and or define/ broaden the sensitive period.

The report emphasized the limitation of the current EPI literature and was quite detailed in highlighting issues with the interpretation of this literature. The panel provided comments and a recommendation for a consistent structure for further review. This reviewer however was also glad to see that the report emphasized that despite limitations in the epidemiological literature "..the SAB notes that there are scientifically sound clinical and rodent toxicology reports that describe the biology linking iodide deficiency, changes in in thyroid hormone production and development and neurobehavioral effects." (Page 9, lines 5 to 7).

These statements then support the suggestions by the SAB review to consider a staged approach to a desired use of a full MOA integrated PBPK and PD model (see page 30 for descriptions).

As the report emphasizes both the modeling and research opportunities in much of its discussion it is significant that it also emphasizes initial steps. Further wording could be added that could clarify if these initial stages could support public health action for intermediate MCLGs. Please clarify.

Regarding the importance and opportunity of developing the integrated PBPD models for thyroid changes the SAB panel identified the opportunity to evaluate other co-exposures to goitrogens with comparable MOAs and lists thiocyanate and nitrate (page 22 lines 36-39). The SAB report could also add a statement that many other chemicals have been considered for thyroid disruption and thus the model would have potentially great utility not only for co-exposures but for unifying other approaches across chemical type for this shared endpoint.

The discussion of the model is detailed and interesting however this reviewer would have liked a few more supportive words on use of distributions for many of the anticipated parameters in the proposed models given the rich clinical, dietary and human data sets on ranges of thyroid levels.

The purpose of the models for determining dose-response relationships between early thyroid hormone alterations and the myriad of growth and neurodevelopmental endpoints (See Figure 2, item 3b page 28) is still unclear. Providing further suggestions and illustration (?) of the integration of Figure 1 (Page 16) and Step 1 from Figure 2 would put focus on the modeling to ensure applicability for its ultimate use for risk assessment. EPA in other contexts discusses the concept of Adverse Outcome Pathways however this review is relatively silent on these concepts. The SAB should consider whether adding this concept would help or confuse this already detailed commentary.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

In general the recommendations proposed for the draft report were well documented in the report and additional information in the appendix provides even further support.

Comments from Dr. Cynthia Harris

An advisory panel (SAB Perchlorate Advisory Panel) was convened by U.S.EPA to provide approaches and recommendations regarding the derivation of a Maximum Contaminant Level Goal (MCLG) for the environmental contaminant, perchlorate. The following narrative represents my comments on the following quality review questions: (1) Were the charge questions adequately addressed? (2) Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report? (3) Is the draft report clear and logical? (4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Quality Review Question #1 – Were the charge questions adequately addressed?

Specifically, the charge questions sought guidance and recommendations regarding the following areas: (a) significance of life stages and should EPA consider life stage factors in deriving an MCLG; (b) determination of the rationale for considering these factors; (c) identification of the strengths and limitations of the described PBPK models and should PBPK modeling be utilized to derive a MCLG for perchlorate; (d) use of epidemiological data (post-NRC data) in deriving the MCLG for perchlorate; and (e) integration and use of a total body of information to derive a health protective MCLG for perchlorate and estimate reductions in health effects by reducing perchlorate in drinking water.

Significance of Life Stages and Rational for Consideration of Life Stage Factors in Deriving an MCLG for Perchlorate

Comments: The panel has conducted a very thorough review of the literature regarding toxicological studies that describe critical adverse effects on early thyroid-dependent brain development, particularly on the fetus and neonates resulting from inadequate iodide uptake and low thyroid hormone levels. The description of how perchlorate inhibits iodide uptake and, subsequently, interferes with thyroid hormone production is clear and scientifically sound. Given the adverse impact on early brain development in the fetus and neonate, in particular (e.g., irreversible neurological and cognitive deficits), as a result of a hypothyroxinemic state, the recommendation to consider the fetus and neonates as sensitive life stages in developing a MCLG for perchlorate is a sound recommendation based on significant data and reports. In addition to the noted sensitivity of the fetus and neonates and potential effect of decreased thyroid hormone on brain development, the report also indicates that infants and children also have increased sensitivity; however, the evidence for these life stages is not discussed to the same degree in this report in the body of evidence provided.

Identification of the Strengths and Limitations of the Described PBPK Models and Should PBPK modeling be Utilized to Derive a MCLG for Perchlorate

Comments: The panel recognized the significance of utilizing a comprehensive biological framework for deriving a MCLG for perchlorate by addressing the mode of action of perchlorate from exposure to neurodevelopmental impacts. Thus, the panel recommended the use of the PBPK/PD-IUI model for integrating exposure with differential biological changes during the

lifestages and prediction of pharmacokinetics. In particular, this model, unlike the earlier model, would link early biological events (e.g., iodide deficiency) with subsequent events (e.g., neurodevelopmental outcomes). This recommendation is indicative of the invaluable utility of this model as a more effective tool in deriving the MCLG for perchlorate as opposed to the formula-based RfD. In addition, the review panel recommended that a communication strategy be developed that documents and described the MOA framework and model for public stakeholders and facilitate understanding of how the MCLG for perchlorate was derived using this model. I strongly support this recommendation given the significance and need for providing clear and basic descriptions of the premise for how MCLGs are derived to public stakeholders.

Use of Epidemiological Data (Post-NRC Data) in Deriving the MCLG for Perchlorate

Comments: While the SAB review found the epidemiological data, post-NRC 2005 report, to be useful in determining the size of potentially sensitive populations in the U.S., estimating extent of exposure to perchlorate and other goitrogens, and estimating source of perchlorate in drinking water among these populations, the panelists concluded that there was a paucity of data to infer an association between perchlorate exposure and thyroid anomalies in pregnant women, neonates or the general population. Factors such as study design, exposure assessment, sample size and statistical modeling have inconsistent when comparing the results from various epidemiological studies. The review panel recommended that existing exposure and biomonitoring studies may be useful for understanding the prevalence of sensitive populations. I believe that the recommendation to conduct prospective studies of urinary biomarkers of perchlorate exposure and thyroid function and childhood neurobehavioral development as well as conducting sensitivity analyses by measuring co-exposures to other goitrogens, would also help inform our understanding of the role of perchlorate in the neurodevelopment of sensitive populations.

Integration and Use of a Total body of Information to Derive a Health Protective MCLG for Perchlorate

Comments: The derivation of the MCLG for perchlorate will be predicated on: (1) delineation of hypothyroxinemic pregnant and lactating women and infants exposed to perchlorate through water-based formula preparations or breast milk (as indicated by determination of sensitive/life stages and impact on early brain development; (2) use of PBPK/PD-IUI modeling and use of a MOA framework to link current biological events with subsequent outcomes; and (3) need for combined analyses and a more robust literature review to support a MCLG on hypothroxinemic pregnant and lactating women. The panel was thorough in their descriptions and recommendation on the use of lifestage data, significance of the PBPK/PD-IUI modeling, and identification of data gaps regarding epidemiological studies and perchlorate exposures. However, the description of how EPA can use the available data to estimate reductions in adverse health effects, despite the aforementioned limitations, was relatively sparse and previous risk assessments, regarding per chlorate, should provide a baseline for more robust discussions and subsequent recommendations.

Quality Review Question #2 – Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

Comments: To my knowledge, there are no significant technical errors or omissions in the report. With the exception of the last segment, discussing estimated reductions in adverse health effects, the report is very thorough and descriptive.

Quality Review Question #3 – Is the draft clear and logical?

Comments: The draft is well-written and based on sound science. The Panel was very effective in being responsive to the charge questions and made realistic and novel recommendations that potentially build on or enhance current tools and methodologies (e.g., focus on MOA and PBPK/PD modeling in deriving the perchlorate MCLG). In addition, the report provides a nice schematic of a proposed MOA model that may be considered in the process.

There was some repetition, throughout the narrative, regarding the association of iodine deficiency with adverse impact on early brain development as well as the general biological steps associated with hypothyroidism. This repetition was not always significantly additive to the merit of the report. In addition, there were some minor typos. For instance, on p. 31, line 4, a sentence reads, "For the purposes of deriving an MCLG for perchlorate, SAB recommends that the EPA focus on measurements relevant to these adverse effects including iodine deficiency and hypothyroxinemia; and …." Thus, the sentence was not finished.

Quality Review Question #4 – Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Comments: Yes, the conclusions and recommendations are supported by the body of the draft report. The recommendations are realistic and informed by current scientific knowledge, technology and tools. The presentation of conclusions and recommendations is very organized and the conclusions and recommendations are responsive to each component of each charge question.

Comments from Dr. Martin Philbert

1. Were the charge questions to the committee adequately addressed?
    a. Overall, the draft report addresses the major elements of the charge questions and formulates a general roadmap for research aimed at determining the thyro-toxic effects of exposure to perchlorate.
    b. The draft report emphasizes the need for research focused on pathophysiological outcomes in "at-risk" populations rather than the use of surrogate measures such as IUI. The emphasis on a functional outcome (thyroid hormone production and PBPK/PD rather than IUI alone) is a well-considered approach and one that more closely maps to public health outcomes.
    c. There is an appropriate emphasis on short. mid-, and longer term research goals that would allow the Agency an opportunity to prioritize and plan.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the report?
    a. The report is thorough and appears to address all of the pertinent issues.
    b. Next to that provided in section 3.4.1 the discussion surrounding *Estimating Reductions in Adverse Health Effects* in section 3.4.2 appears to be somewhat terse. It is not clear from the draft report whether or not the apparent brevity of this section is due to the lack of available data or some other pertinent consideration.

3. Is the draft report clear and logical?
    a. The draft report is generally well written, however, repetition (especially those referring to the 2005 NRC report) permeates the letter to the administrator, the executive summary and the body of the report. Light editing of the draft will address the issue of repetition and the typos scattered through the document.
    b. The identification of *fetuses, neonates and infants* as the most sensitive life stage is appropriate based on the evidence. However, as written, the distinction between life stage and sensitive populations is confusing (*pregnant and lactating women, and infants*… in the latter case).
    c. As a relative neophyte in the area of epidemiology, the committee is to be congratulated on the clarity of discussion in this area.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
    a. The recommendations are appropriately supported by the available evidence. No concerns are identified.

Comments from Dr. Paige Tolbert

The following comments are provided in my role as discussant/quality reviewer of the advisory report by the SAB Perchlorate Advisory Panel responding to EPA's request for SAB advice on approaches to derive a maximum contaminant level goal for perchlorate (draft advisory report, February 25, 2013.)

Quality Review Question #1: whether the original charge questions to SAB Panel were adequately addressed.

Response:
The SAB Panel has done an excellent job addressing the original charge questions posed to them by EPA. The charge questions solicited guidance on the following matters:

- how EPA should consider life stage factors in deriving an MCLG for perchlorate;
- how EPA should consider PBPK modeling in deriving the MCLG, including consideration of two sets of model results;
- how EPA should consider epidemiologic data reported since the NRC 2005 monograph in deriving the MCLG;
- how EPA can best use the total body of information to derive the MCLG, while using epidemiologic and biomonitoring data in establishing bounds;
- how EPA can use available data to estimate reductions in adverse health effects likely to result from reduction of perchlorate in drinking water.

The Panel has provided a thoughtful and rigorous response to each charge question and a number of helpful suggestions. The Panel presents well-founded guidance regarding considering sensitive life stages explicitly, using a mode of action approach that incorporates our understanding of differences across life stages. The Panel recommends the use of PBPK/PD modeling of iodide uptake inhibition and advises that an expanded approach be pursued to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes. The Panel recommends specific ways in which data from epidemiologic and biomonitoring studies can be used (NB: I have a couple of comments regarding the appendix on use of epidemiologic data noted in Quality Review Question #2, below). Finally, the Panel finds that there are insufficient epidemiologic data available to estimate reduction of adverse health effects attributable to reduction of perchlorate in drinking water, but recommends some initial steps to move toward this goal.

Quality Review Question #2: whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report

Response:
In general, I did not find technical errors, omissions or issues that are inadequately dealt with in the report. There are a couple of exceptions, however. While I felt that the appendix presenting the panel's views regarding the epidemiologic evidence was generally very strong and methodologically rigorous, I take issue with two points.

First, on page B-2, the panel describes studies that define exposure based on group level characteristics, such as water district, as being a variation on the ecological study design. The panel concludes that, "the four studies examining ecological measures of perchlorate exposure in drinking water in relation to thyroid function, regardless of whether or not they show an association, are of little value for guiding decisions regarding a MCLG for perchlorate in drinking water." The basis for dismissing these studies does not appear to be well-founded and the rationale needs to be revisited. Whereas the panel is correct that such studies can be viewed as ecological when the research question relates to personal intake of perchlorate, there is a second important framework for looking at these studies that appears to have been overlooked. If the "exposure" of interest is defined as municipal water supply levels, these studies can provide important evidence that may be useful for certain purposes, assuming they have been done well (e.g., sufficiently powered, confounders and effect measure modifiers appropriately handled, models well-specified...) These studies may provide key evidence regarding the public health impacts of varying levels of perchlorate in municipal water supplies, inherently accounting for the fact that individuals modify their exposures to perchlorate through such actions such as drinking bottled water and ingesting perchlorate-containing foods, and as such these studies are potentially useful in the overall assessment. [This is analogous to the rationale for studying ambient levels of pollutants in different areas to assess the public health impact of varying levels of ambient pollution, accounting for the fact that people modify their personal exposure via such factors as air conditioning, and the fact that they receive exposure to these pollutants from other sources such as indoor sources; these types of studies form a key evidentiary basis for setting ambient air quality standards. See, e.g., Sheppard et al, J Exp Anal Environ Epidemiol 15:366-376;2005.] While I agree that for the purpose the panel was considering, these studies do not provide useful quantitative information to be used as direct input into the PBPK/PD modeling undertaking, these types of studies (if they are done well) can potentially provide complementary evidence and a reality check on the ultimate recommendation for the MCLG derived using output of the PBPK/PD modeling.

A second issue that I think warrants tweaking is the discussion on page B-6 regarding adjustment for factors that are associated with the outcome and not with the exposure. The discussion leaves the impression that adjustment for such factors will lead to loss of precision. It should probably be acknowledged that there is a trade-off in impact on precision between having extra parameters in the model and reduction of the error – if the factor is a strong predictor of the outcome this will tend to favor its inclusion in the model and increase the precision of the measure of effect of the main exposure of interest.

Other than these issues, I found the appendix to be an excellent review of the issues associated with use of the existing epidemiologic data. I found the incorporation of DAG-types of thinking in the guidance to be especially helpful. The recommendations for future work appear appropriate. While the possibility of reanalyzing data from existing studies to handle some of the concerns about model misspecification and to incorporate improvements in the biological understanding was raised in the body of the appendix, it did not rise to the level of a recommendation; I wonder if the panel might want to add this to the recommendations. Does the panel feel that reanalysis would be a productive undertaking, or are the existing studies too limited due to design issues?

Quality Review Question #3: whether the Panel's report is clear and logical

Response:
Overall, I found the Panel's report to be clear and logical. The report effectively communicates the Panel's guidance with respect to EPA's charge questions. The report is well-written and scientifically sound.

Additional editorial comments:

Add a first paragraph to the letter that provides the purpose of the letter, along the following lines: that on behalf of the SAB we are transmitting the advisory report in response to EPA's request for guidance on approaches to derive a maximum contaminant level goal for perchlorate, in response to EPA white paper, "Life Stage Considerations and Interpretation of Recent Epidemiologic Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate," dated May 18, 2012…

Line 34 of p.1 and line 25, p.6 – identify the white paper the first time it is referred to, i.e., "Life Stage Considerations and Interpretation of Recent Epidemiologic Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate" (May 18, 2012)

Typos:
line 45, p.2 of letter
line 10, listing of Perchlorate Advisory Panel membership
line 23, p.10 of draft advisory report
line 7, p.22
line 24, p.27
line 5, p.33
line 8, p.B-7

Quality Review Question #4: whether the conclusions drawn or recommendations provided are supported by the body of the Panel's report

Response:
The conclusions drawn and recommendations provided are supported by the body of the Panel's report. Overall, the Panel's conclusions and recommendations are scientifically sound and well-justified. The Panel did an excellent job.

Comments from other SAB Members

Comments from Dr. Joseph Arvai

General comments:

I appreciate that a great deal of work went into this report. Even though this is not my area, I found the report to be well written and easy to follow.

In terms of a general comment, I found the first sentence of the letter to the Administrator to be unnecessarily affective (ditto the first sentence on page 18). We can infer from the report – easily, I might add – that perchlorate is to be taken seriously by the EPA. There's no need for the report to refer to "rocket fuel, fireworks, flares, and explosives". It reminds me of the "dihydrogen monoxide" hoax. These respective sections should, in my opinion, start with "The Environmental Protection Agency identified perchlorate as a potential…".

1) Were the charge questions to the committee adequately addressed?

Yes.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

To the best of my knowledge, no.

3) Is the draft report clear and logical?

Yes

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

As far as I can tell, yes.

Comments from Dr. Thomas Burbacher

1) Were the charge questions to the committee adequately addressed?
Most of the charge questions were adequately addressed. For some of the questions, there seemed to be more of a focus on recommendations for future studies than on addressing the specific question. For example, the response related to the sensitive life stage question regarding intrauterine exposure to perchlorate and the impact on thyroid status in fetuses included several appropriate recommendations for future studies but it did not address the issue of how EPA should consider this issue in their deliberations. Suggestions for future studies are included in nearly all of the responses and this is appropriate. Responses should be reviewed, however, to ensure that the questions are addressed adequately while providing critical information related to future studies.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
I did not observe any technical errors. In terms of omissions, there are several critical issues discussed where quantitative information should be provided whenever possible. Discussions of studies reporting perchlorate effects should include dose-response information. Discussion of studies indicating developmental effects related to iodine deficiency or thyroid hormone deprivation during pregnancy should also include quantitative information on the timing and level of deprivation and the extent of developmental effects whenever possible. This information will provide the reader with some context regarding the sensitivity of these effects to perchlorate exposure.

3) Is the draft report clear and logical?
Overall, the draft is clear. The draft, however, should be reviewed to reduce repetition.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?
For the most part, the conclusions drawn or recommendations provided are supported by the body of the draft report. I am confused, however, by the recommendation that “the sensitive populations for perchlorate exposure are hypothyroxinemic pregnant and lactating women and infants exposed to perchlorate through either water-based formula preparations or breast milk”. The reviewers indicate that this recommendation should replace the NRC recommendation of “the fetuses of pregnant women who might have hypothyroidism or iodide deficiency”. Are the reviewers indicating that pregnant and lactating women are part of the sensitive population or is it the fetuses of hypothyroxinemic pregnant women and the infants of hypothyroxinemic lactating women? As it reads, the statement would seem to exclude fetuses, which would not make sense. This recommendation is repeated several times in the report so it is very important that it be clear.

Comments from Dr. Thomas Burke

General comments:

The report is very well written and represents an advance in the application of science in the development of the MCLG. The recommendations of the Committee are consistent with NAS "Silver Book" recommendations for improving consideration of susceptibility an applying MOA and PBPK modeling.

I am concerned that the report may lead to further delays on moving ahead with efforts to reduce perchlorate exposures. The committee recommends that EPA expand the PBPK approach to move beyond IUI to specific predications of thyroid hormone, and recognizes that this may take years. Given the large number of susceptible women and children, and the ubiquitous nature of the exposure is this delay in developing the MCGL acceptable to the committee and EPA? Should an interim approach be applied?

1) Were the charge questions to the committee adequately addressed?

The charge questions were generally well addressed. The report falls short of recommending an approach to identifying a specific POD from which to derive a health protective MCGL. More detail may be needed to describe more specifically the recommended "integrated approach". Will this approach yield multiple critical dose levels or a distribution of potential PODs for different life stages? How would these results then be used to select a BMD or other POD as the basis for a MCGL?

Similarly, the question on quantifying reduction of adverse health effects is challenging. The traditional RfD approach does not provide such an estimate of reduced health impacts. Perhaps the report should provide more specifics on estimating the reduction in the "risk" of exposure on the most sensitive population. Improved estimates of the number of women pregnant and lactating women who are at risk from drinking water exposures could be provided.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

There are no apparent technical errors or omissions.

3) Is the draft report clear and logical?

The draft is very clear and logical.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions and recommendations are well supported throughout the report.

Comments from Dr. George Daston

We were asked to address four specific questions as part of the quality review.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;
2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. whether the Committee's report is clear and logical; and
4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

Question 1: I believe that the charge questions were adequately addressed, although I would have liked to have seen a little more detail on whether there are studies published since 2005 that call into question the conclusions of the NRC report. EPA charged the SAB committee with evaluating the literature since 2005. My inference from reading the report is that post-2005 literature provides support for considering pregnant women, their fetuses and newborns as the most sensitive subpopulation. I did not see in the report that there was new literature that suggested a lower NOEL for perchlorate, or additional/ new insight into the mechanism of perchlorate toxicity.

Question 2: I did not note any technical errors or omissions.

Question 3: The report was logical and reasonable. The report supports using maternal hypothyroxinemia as the critical effect for risk assessment, vs. the NRC recommendation of iodide uptake inhibition. Since these two events are mechanistically linked, it would be useful to have more of an explanation as to why hypothyroxinemia is preferred.

Question 4: The conclusions and recommendations are supported by the body of the report. The use of a combined PBPK and pharmacodynamic model makes a great deal of sense and may serve as a precedent for future mode of action-based risk assessments.

Comments from Dr. Costel Denson

1. Were the charge questions adequately addressed?
Four sets of charge questions are presented. Each set was adequately addressed.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?
All issues were adequately dealt with in the report.

3. Is the draft report clear and logical?
The draft report is judged to be clear and logical.

4. Are the conclusions drawn or recommendations provided supported by the body of the report?
The conclusions drawn and recommendations are supported by the report.

Comments from Dr. Otto Doering

Were the Charge Questions adequately addressed? The charge questions appeared to be quite narrow and appeared to be addressed.

Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report? I could not identify any technical errors or omissions. I would appreciate a discussion of the concerns raised in this respect by some of the public commenters.

Is the draft clear and logical? Given the narrow specificity of the questions and the kind of responses thus required, the draft appeared clear and logical in its responses. However, again I am concerned in this respect by the questions raised by public commenters.

The conclusions drawn and recommendations provided appear to be supported by the body of the report.

Comments from Dr. Joel Ducoste

Quality Review summary:

1) **Were the charge questions to the committee adequately addressed?**
   Overall, the charge questions were addressed in the document. Specific comments about the report include the following:

   a) The third paragraph in the administrator letter that describes the NRC recommendations could be deleted as is it discussed in the report.
   b) Section 3.1.3 is missing a recommendation subsection as was done for the other subsections
   c) On page 16, the charge question: "What are the strengths and limitations of the two PBPK model results described in this effort?" should be removed from here since it is addressed on page 19.
   d) In section 3.3., directed acyclic graphs (DAG) was suggested as a method to determine causal relationships among variables. However, depending on the quality of the data, DAGs may not be able to develop strong robust relationships. It may be fruitful to apply more than one correlation technique. Suggested alternatives include the following:

      Weighted Co-expression Network Analysis:
      Langfelder P, Horvath S: **WGCNA: an R package for weighted correlation network Analysis,** *BMC Bioinformatics* 2008, **9:**559

      Context likelihood of Relatedness:
      Faith JJ, Hayete B, Thaden JT, Mogno I, Wierzbowski J, Cottarel G, Kasif S, Collins JJ, Gardner TS: **Large-scale mapping and validation of Escherichia coli transcriptional regulation from a compendium of expression profiles, PLOS Biology 2007, 5(1), 54-66**

      Algorithm for reconstruction of Accurate Cellular Networks:
      Margolin AA, Nemenman I, Basso K, Wiggins C, Stolovitzky G, Dalla Favera R, Califano, A: **ARACNE: an algorithm for the reconstruction of gene regulatory networks in a mammalian cellular context, BMC Bioinformatics 2006, 7:S7**

      Minimum Redundancy/Maximum relevance Network:
      Meyer PE, Kontos K, Lafitte F, Bontempi G: **Information-theoretic inference of large transcriptional regulatory networks, EURASIP J Bioinform Syst Biol. 2007:79879**
      Signed DAG:
      Vanderweele, T.J., Rbins, J.M., **Signed Directed Acylic Graphs for Causal Inference, J Royal Statistical Society 2010, 72, pp.111-127**

2) **Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?**
   Please see response to point 1 above.
3) **Is the draft report clear and logical?**
   Yes, overall.
4) **Are the conclusions drawn or recommendations provided supported by the body of the draft report?**
   Yes, overall

Comments from Dr. David Dzombak

I commend the panel on a thorough evaluation that is responsive to a complex set of charge questions. The specific advice offered will be valuable to the EPA in moving forward with deliberations regarding establishment of an MCLG for perchlorate.

1. Were the original charge questions adequately addressed?

   Yes, the original charge questions are addressed adequately.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Panel's report?

   I found no technical errors or omissions.

3. Is the Panel's draft report clear and logical?

   The draft report is well written. The body of the report responds to the charge questions systematically. The advice offered by the SAB is in the context of responding to a relatively long list of specific charge questions from the EPA.

   The relationship of the specific SAB advice to specific charge questions from the EPA does not come across in either the Letter to the Administrator, or in the Executive Summary, however. Those two sections, while well written, give the impression that the report presents a self-initiated study by the SAB. Indeed, the word "charge" is not used at all in either the Letter or the Executive Summary. This is an important shortcoming that must be addressed in revision.

   Both the Letter and the Executive Summary need to be revised to make clear that the report presents responses to specific charge questions from the EPA. It would not be appropriate to repeat the charge questions in the Letter, but the charge should be summarized there. In the Executive Summary, the key charge questions should be listed as headers for relevant sub-sections, as done in the body of the report.

   I suggest that a change be considered for the title of the SAB effort given in the subject line of the Letter to the Administrator, so that the report does not appear to be a self-initiated SAB study. In my view, the title in the subject line should be closely related to the title of the charge to the SAB given in Appendix A.

4. Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?

   The conclusions and recommendations are adequately supported in the body of the report. However, as described in Section 3 above, the relationship of the specific SAB advice to specific charge questions from the EPA does not come across in either the Letter to the

Administrator, or in the Executive Summary. This is an important shortcoming that must be addressed in revision.

Comments from Dr. Taylor Eighmy

Overall Comments:

1. General Thoughts:

The SAB has been asked to provide an advisory report to the EPA on efforts by the agency to establish an MCLG for perchlorate using recent information and the 2012 white paper on perchlorate health effects that followed on the seminal 2005 NRC report on *Health Implications of Perchlorate Ingestion*. The SAB has determined that there is sufficient information to derive a perchlorate MCLG using a MOA approach and PBPK/PD-IUI modeling rather than the traditional RfD approach. This is a novel approach compared to RfD methodology examined in the 2005 NRC study.

The advisory effort does an excellent job of articulating how the MOA approach and PBPK/PD-IUI modeling can be used by EPA to set an MCLG. This is a novel approach and the mention about a "stepwise "integrated" approach is a logical way forward" is appropriate.

This is a complex matter with significant implications to the water industry. Even though the four charge questions from the EPA are quite narrow and explicit (e.g., how best to consider recent information on sensitive life stages, epidemiological and biomonitoring studies; the agency's PBPK modeling efforts; and approaches to use and integrate this information), I believe that some context as to the impact of the MCLG on the water industry should be mentioned in the introduction section even though it is outside the charge.

2. Mapping the Report to the Letter to the Administrator and to the Executive Summary:

I believe that the letter to the Administrator would benefit by calling out what really is a four-part charge as a separate paragraph (see line 2 of page 2 of the letter).

Generally, the letter, executive summary and the body of the report map well with regard to the background, charge, response to the charge, and summary recommendations.

3. Report Organization:

The report is well organized and clear to follow and aligns well with the seven charge questions.

Response to the Four Specific Questions:

1. Were the original charge questions to the Panel adequately addressed?

I believe that all four charge questions were adequately addressed.

2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with?

From my perspective, no.

3. Is the report clear and logical?

I found the report to be very clear and logical.

4. Are the conclusions drawn or recommendations provided supported by the body of the report?

From my perspective, yes.

Comments from Dr. Robert Johnston

1) Were the charge questions to the committee adequately addressed?

Yes, the report appears to do a good job of responding to the charge questions. The report not only provides clear advice for a long term research agenda to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure, but also details an interim approach that can be taken by the Agency to relate iodide uptake inhibition to thyroid hormone perturbations. I found the combination of short-term and long-term advice to be useful, particularly given current limitations in our ability to forecast potential adverse outcomes. I was impressed by the clarity and level of detail in the report's recommendations (while also noting that this is an area in which I am not an expert).

One minor comment is that the response in section 3.4.2, Estimating Reductions In Adverse Health Effects, is more brief than responses elsewhere in the document. The charge question is addressed here as well, but this section provides less detail than others in the document. Given that this report is outside of my area of expertise, I cannot ascertain whether the seemingly missing detail is relevant.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

To my knowledge, there appear to be no technical errors or major omissions in the report.

3) Is the draft report clear and logical?

Yes, the report is clear and logical, and does a good job linking responses/recommendations to specific charge questions and recognizing current capacities and limitations of the science. There is some repetition in the report, which could perhaps be reduced through judicious editing.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions and recommendations are supported by the body of the report. The report appears to be well grounded in findings from the 2005 NRC report on the health implications of perchlorate ingestion, along with documented research that has taken place since that time.

Comments from Dr. Kimberly Jones

1. **Were the original charge questions adequately addressed?**

   Yes, the original charge questions were adequately addressed.

2. **Are there any technical errors or omissions in the report of issues that are not adequately dealt with in the Panel's report?**

   I did not see technical errors or omissions in the report.

3. **Is the Panel's draft report clear and logical?**

   The draft is written very clearly.

4. **Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?**

   Yes, the recommendations link well to information presented in the body of the report.

General Comments:

The report is well written, and the committee should be commended for presenting this information in a logical, clear manner. My comments are primarily editorial but may help in overall understanding of the report.

1. In the Executive Summary, last paragraph (p. 4), the report recommends a "stepwise "integrated" approach" to allow multiple sources of information to be integrated into the MCGL derivation. This sentence is unclear in context, as it was a cut/paste from the body of the report. It needs a sentence or two of supporting information in the Exec Summary. The EPA report lists integration of information as one of the four overarching issues to be considered, but the text of the report may be referring to the steps in Figure 2 (p. 28). This should be clarified in the Executive Summary.

2. The outline formatting on page 16 is confusing, as section 3.2 lists a charge question without any supporting text, followed by a new section with the other charge question in that section. This charge question is then repeated on page 19.

3. There are two sub-questions that don't have specific recommendations attached – section 3.1.3 (Differences in greater severity….compared to adults) and in section 3.4.2 (How can EPA use the available data to estimate…..in drinking water). There may not be a need to directly construct a recommendation for each portion of the charge question, but those were two that did not have a direct recommendation.

Comments from Dr. Bernd Kahn

The SAB Panel review of the SAB advice on MCLG for perchlorate is very well done. My responses to the four questions are, respectively, yes, no, yes, and yes. I have the following specific suggestions:

1. Letter to the administrator: The letter should be considerably shorter and more to the point by crisply stating the main advice. At present, the letter appears to be a cut-and-paste product of the Executive Summary and the Introduction.
2. P.30, l.38 on: The earlier discussion of goitrogens on the bottom of pages 22 and 24 suggests that it is important to consider perchlorate concentration and effect in relation to other goitrogens (nitrate, etc.) in water. If perchlorate typically has a minor effect relative to the others, reducing its concentration may accomplish nothing.

Comments from Dr. Catherine Karr

1) The panel responded adequately to each charge question
2) I observed no technical errors or omissions or issues not adequately dealt within the draft report
3) The report is clear and logical. There is some repetition but overall serves appropriately to highlight key messages such as the delineation of the three sensitive subpopulations and the application of an MOA based on established linkages and application of toxicological and clinical data. The use of figure 2 and examples of short and longer term approaches to incorporating these data were helpful approaches.
4) The recommendations are easily identified and adequately supported in the body of the report.

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Comments from Dr. Nancy Kim

1. Were the charge questions to the committee adequately addressed?
   Yes.
2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
   For the most part, no (see comments under question 3).

3. Is the draft report clear and logical?
   For the most part, yes.

Letter to the Administrator

The Letter to the Administrator provides background information on perchlorate, the NRC report, the MCLG process and EPA's white paper. It gives two conclusions reached by the SAB (page 2, lines 2 – 7), but does not provide any of the SAB's recommendations. The Letter needs to be expanded to provide more highlights from the SAB's report, especially its major recommendations.

Body of the Report

a. The report states the following: "The SAB finds that the most sensitive life stages are the fetus, neonates and infants because these are the stages when thyroid-dependent brain development occurs. Thus, the sensitive populations for perchlorate exposure are hypothyroxinemic pregnant and lactating women and infants exposed to perchlorate through either water-based formula preparations or breast milk." I understand the distinction that is being made between most sensitive life stages and the sensitive populations for perchlorate exposure. Keeping these two sentences together is important. However, the wording may be too subtle. Adding some additional explanation might be useful.
b. Section 3.1.3 provides much useful information for EPA. Should the SAB report have a recommendation section in 3.1.3?
c. Several places in its report, the SAB makes recommendations about research that should/could be carried out. If the SAB provided specifics with the recommendation about why the research is important or necessary, including if the research results are needed for developing a scientific defensible MCLG versus providing more information about perchlorate's toxicity, that might be useful for EPA. (See page 13, line 37-38; page 15, lines 40-44, page 25, line 33-35,).
d. Page 13, line 42 and page 14, lines 1-3. This sentence may need some editing. Wouldn't the fetus also have less thyroid hormones early in pregnancy if maternal thyroid hormones are lower? The sentence can be interpreted to imply that fetal supplies are only reduced later in gestation which seems inconsistent with the paragraph beginning on page 15, line 7.
e. Page 18, line 23, Recommendation. Can additional advice be given about which of the following needs to be done before the MCLG can be developed and what can be done

subsequently? That may be covered in the material given on page 30, lines 17-26. If so, adding a statement here about time lines being described on page 30 would be useful.

f. Page 27, lines 20-30. The flow of this paragraph seems awkward. The first sentence mentions "the following MOA-based approach." The reader expects that the next sentence will be about the approach and that doesn't happen. Then line 28 mentions that "the approach is discussed below and summarized in Figure 2," which is reminiscent of the first sentence in the paragraph. Some minor editing would improve it.
g. Page 28, line 4 under Step 1. It might be useful for the reader to point out if this is the same as the NRC recommendation or alternatively what the differences are with the NRC recommendation.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
   In general, yes (see comments under question 3).

Minor comments

1. Page 10, line 15. Should "from the first trimester" be "for the first trimester?"
2. Page 14, line 11 "hormone (TRH) and (TSH)" should probably read "hormones (TRH) and TSH)).
3. Page 16, line 16. Need space between by and RAIU.
4. Page 22, line 7. Targeting should probably be targeted.

Comments from Dr. Francine Laden

1) Were the charge questions to the committee adequately addressed?

The charge questions to the committee were adequately and thoroughly addressed.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not identify any technical errors or omissions or issues that were not adequately dealt with.

3) Is the draft report clear and logical?

The draft report is well written, clear and logical. The authors did a good job of presenting the numerous topics and questions comprising the charge. Both the Letter to the Administrator and the Executive Summary are well written and nicely summarize the key findings and conclusions of the report. However, although the Executive Summary is organized clearly by the major topics of the charge, t it is not obvious what specific questions were being answered. Perhaps the questions could be summarized in this document as well as the letter to the administrator?

I focused on the main body of the report and on Appendix B, the review of the epidemiologic literature. This section is very well written and provides a good critical review of the literature. At the risk of increasing the repetitiveness of the report, a conclusion section summarizing the main conclusions of this review would be helpful at the end of the Appendix.

One other minor comment, on page B-7 line 1, collider-stratification bias is referred to. This term comes from the causal inference literature which all readers may not be familiar with. It warrants further explanation and definition. Similarly, the term "directed acyclic graphs (DAGs)" comes up on page 24 line 8 in the body of the report. They are not mentioned in Appendix B at all. It would be appropriate to expand on this concept further and explain why they would be a useful tool for this literature.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations are supported by the body of the draft report.

Comments from Dr. Cecil Lue-Hing

General comments

The topic was well researched and the Panel did a very good job of discussing the issues related to perchlorate ingestion via food and public drinking water supplies.

Specific comments

Letter to the Administrator

The letter is informative as an overview of the background and assignment, but does not highlight the major recommendations the way they deserve to be.

On line 6 page 2; suggest(1) edit – The SAB's conclusions and recommendations are **highlighted here, and detailed** in the enclosed report.
Suggest (2) – proceed to highlight the major recommendations in the letter.

Editorial line 20 page 1; try public **drinking** water systems – Note: drinking water is correctly used extensively in the text

The Executive Summary

To this non-toxicologist, the Executive Summary presents a brief but excellent discussion of the issues under review, including some of the Panel's findings and conclusions. However, it would be more informative, if in addition, it also highlighted some of the Panel's major recommendations.

The Body of the Report

The report is well written and demonstrates the Panel's expertise in the subject matter.

Quality Review Questions

1 – Were the original charge questions to the committee adequately addressed? –
Yes

2 – Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?
None that I could identify

3 – Is the Panel's draft report clear and logical? and
Yes

4 – Are the conclusions drawn or recommendations provided supported by the body of the Committee's report
Yes

Comments from Dr. Elizabeth Matsui

(1) Are the charge questions adequately addressed? -YES
(2) Are there any technical errors or omissions - NO
(3) Is the draft report clear and logical?

The draft is generally clear and logical, but may benefit from including a brief diagram or table listing the various clinical tests of hypothyroidism (fT4, TSH, T3) and how they relate to one another. This table/diagram could also including explicit definitions of some of the clinical terms used (hypothyroidism and subclinical hypothyroidism), the terms used in this report ("deficiency" and "insufficiency" of thyroid hormone), and how these terms relate to one another.

In addition, there is a published, albeit small, scientific literature on subclinical hypothyroidism in children suggesting that treatment of these children with elevated TSH, but normal fT4 who have no evident clinical effects of hypothyroidism, results in improved growth and neurodevelopmental outcomes (Bona 2013; van Trotsenburg 2005). These findings provide additional evidence of the potential health effects of even subtle changes in thyroid function among children. Lastly, although the report explicitly addresses the link between subtle changes in thyroid function and health effects in the main body of the report, this concept is not clearly stated in the executive summary.

Bona G, Prodam F, Monzani A. Subclinical hypothyroidism in children: natural history and when to treat. J Clin Res Pediatr Endocrinol. 2013 Mar 4;5 Suppl 1:23-8.

van Trotsenburg AS, Vulsma T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, Tijssen JG, de Vijlder JJ. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. J Clin Endocrinol Metab. 2005 Jun;90(6):3304-11.

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(4) Are the conclusions/recommendations supported by the body of the draft report? - YES

Comments from Dr. Surabi Menon

Q1: Were the charge questions to the committee adequately addressed?
The charge questions appear to have all been addressed very thoroughly, drawing a lot from available literature to make the necessary recommendations.

Q2: Are there technical errors or omissions or issues that are not adequately dealt with in the draft report?
There were no particular errors in the draft report that I could identify. Please note that is not a subject matter I am familiar with, so it was hard to understand if errors or omissions were present.

Q3: Is the draft report clear and logical?
The report appears to be logical and mostly clear.

Q4: Are the conclusions drawn or recommendations provided supported by the body of the draft report?
The recommendations appear to be well supported by the body of the report. Most of the studies presented appear to be U.S. based cases. It might be useful to note if similar work has been undertaken in other countries and how that might support the recommendations.

Comments from Dr. James Mihelcic

1) Were the charge questions to the committee adequately addressed?
Yes

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
No

3) Is the draft report clear and logical?
Yes

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Yes

Minor Formatting Comments
Page 21, line 41: µgkg/day and page 22, line 17: written as µgKg/day
Pg 41, line 29: J Neuroendocrinol. Requires italics

Comments from Dr. Eileen Murphy

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes. I think the distinction that the SAB put on most sensitive life stages versus sensitive populations is important. Also, justification for expanding the NRC recommendation of "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" with "fetus, neonates and infants" is fully presented. The different between sensitive life stages and sensitive populations is subtle but significant. I think the SAB presents the subtly and emphasizes the difference throughout the report.

EPA seemed particularly interested in studies published after 2005 and whether results in these subsequent studies validated those from earlier studies (and hence the NRC conclusions). I thought the information on these later studies could have been better emphasized and compared to the earlier studies. It was not clear in reading the report whether the SAB was providing a summary of all the studies including those published after 2005 or separating them. Prioritization of the latter studies is unclear as well. Because the charge questions distinguish this, I think the report should better emphasize the difference.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

None that I could see, though I am not expert in this field.

3. Is the Committee's report clear and logical?

Yes. I found the report very well organized and clear.

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes. One item, however, where I don't think the SAB fully justifies a recommendations is the recommendation to delay "on the order of one to several years" the development of an MCLG in order to expand the EPA PBPK/PD approach past IUI to explicitly incorporate predictions of thyroid hormone. Rather, evidence is provided in the report to justify moving ahead to the development of the MCLG. I think the SAB meant to recommend this step as a simultaneous activity rather than to delay MCLG development, and that should be clarified.

Comments from Dr. James Opaluch

Were the charge questions were adequately addressed?

I believe the report is highly responsive to the Charge to the Committee.

Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?

The topic of this report lies outside of my area of technical expertise, but I didn't see any technical errors or omissions.

Is the Panel's report is clear and logical?

Yes, the report is logical and clear. I found I could follow the report, despite not being an expert in the area.

Are the conclusions drawn or recommendations provided supported by the body of the Panel's report

The conclusions are well supported by the body of the report.

Typos:
Letter to the Administrator, page 2, line 45, "from ~~the~~ all the available"
Report, page 10, line 23 "finding<u>s</u> demonstrate"
Report page 27 line 24. There are two periods at the end of the sentence.

Comments from Dr. Amanda Rodewald

1. Were the charge questions adequately addressed?

Yes

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

No. One minor mistake was on page 16, lines 3-4: the charge question seemed to be out of place because it was repeated on the top of page 19.

3. Is the draft report clear and logical?

Yes. I especially liked their use of Fig. 2 to visually represent the recommended approach.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes. Appendix B, which provides a critique of recent epidemiological data was a useful source of additional support for recommendations.

Comments from Dr. Daniel Stram

1) Were the charge questions to the committee adequately addressed?

The charge questions seemed to be addressed quite thoroughly

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not see any technical errors.

3) Is the draft report clear and logical?

Yes although somewhat technical and complex most concepts were explained clearly. I felt as an outsider to this topic that I had learned greatly from reading the report. The report recommends that the EPA should expand the PBPK/PD approach past iodide uptake inhibition to explicitly incorporate predictions of thyroid hormone. I see this recommendation as implying that the MCLG should be based on (modeled) potential for thyroid hormone reductions rather than explicitly on IUI. Is this the intention of SAB? If not then this may need more clarification.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The recommendation that the EPA should expand the PBPK/PD approach past iodide uptake inhibition to explicitly incorporate predictions of thyroid hormone is well supported; the report is convincing that this can be done in a reasonable time period (one to several years).

Comments from Dr. Peter Thorne

1. Were the charge questions adequately addressed?

This is a well-written report that very thoroughly addressed the charge questions.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

The designations of perchlorate intakes on page 22, lines 17, 29 and 30 have incorrect units.

On bottom of page 14 to top of page 15 there is discussion on the MOA and thyroid function with reference to hippocampal synaptic function. It would be helpful to state how lower T3 and T4 levels in the developing fetus impair brain development related to hippocampal function.

3. Is the draft report clear and logical?

The report is logical and clear for the most part. There is some repetition in the draft that could be eliminated perhaps through some reorganization or through a more elaborate figure than that on page 16 showing maternal and fetus/infant exposure routes and mechanistic features. It seems that the effect of perchlorate ingestion through breast milk or infant formula and the resulting reduction in the infant's thyroid hormone synthesis and the role of iodide and maternal exposure is presented multiple times.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The report makes a strong case for designating the sensitive population for perchlorate exposure as the "hypothyroxinemic pregnant and lactating women and infants exposed to perchlorate through water-based formula preparations or breast milk." The report clearly states how the available science has expanded since the 2005 NRC report to support this alternative designation.

Comments from Dr. Jeanne VanBriesen

1. **Were the charge questions to the committee adequately addressed?**

The report provides input on all the charge questions; however, in many cases the response discusses the need for further study and indicates the foci for those studies rather than directly addressing the issue of 'how' the EPA should use the existing information in deriving a MCLG. For example, charge question 1 asks for advice on how EPA should consider life stage factors in deriving a MCLG. The response describes the importance of the life stage factors listed but does not provide guidance to EPA on how to deal with the uncertainties in these different factors and move forward with a MCLG. While interesting and supportive of the need to consider these factors, the details provided are not responsive to the charge question, and the recommendations given do not provide the detailed guidance requested.

Charge question 2 related to the PBPK model assessment and was adequately addressed. The SAB supports the use of percent IUI as a surrogate within the MOA framework to determine a MCLG. However the component of the question on 'how' is only lightly touched on in this section, with recommendations for better model parameter justification and care with communication of results.

Charge question 3 related to the consideration of post-NRC epidemiology data is adequately addressed. It is not clear why the in depth review of these data is relegated to Appendix B since this information is directly responsive to the charge question.

Charge Question 4 related to the use of the total body of information in deriving a MCLG is adequately addressed. The proposed stepwise integrated approach is different from the approach EPA proposes. The SAB correctly identifies that the data provided were insufficient for the SAB to comment on bounding approaches related to the full body of epidemiological data available.

Charge Question 5 related to use of available data to estimate reduction in adverse health effects associated with reducing perchlorate levels in drinking water is addressed; however, the SAB concludes that data are insufficient to provide guidance in response to this charge question. The SAB does provide guidance in how sufficient data can be collected and analyzed to provide insight on the target question.

2. **Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?**

There are no specific technical errors or omissions. The structure of the report makes it difficult to find supporting information for some of the conclusions and recommendations (discussed below).

3. Is the draft report clear and logical?

The structure of the report is challenging, with many sections containing repetitive information about the effects of thyroid disruption on health of infants. It is not always clear why this information is relevant to the specific charge question in the section.

The inclusion of neonates and infants within sensitive sub-populations is discussed in several places, but details are not always provided before recommendations. The Recommendation on page 10 is not supported by content in the proceeding section 3.1.1. Additional information (studies since 2005) is presented related to pregnancy-induced effects related to iodide and hypothyroxenemia; however, no new data associated with infants exposed to perchlorate through formula or breast milk. Later, in section 3.1.3, neonates, infants and young children are mentioned again, but no new data or studies are cited specific to this age. Studies do exist that consider breast-feeding and bottle feeding; however, these are not cited in this section (e.g. Leung et al, 2012). Instead, they appear in 3.3.1 later. If no new information was available specific to neonates and infants, it is not clear why the SAB would expand the sensitive target population beyond the prenatal period. Thus, it is important that supportive studies and information is discussed before this recommendation.

Page 13, lines 30-31. It is not clear based on the preceding paragraph why the SAB is advising the EPA to consider lower thyroid hormone reserves and shorter retention or half-lives in comparison with the non- pregnant adult. The paragraph was focused on the lack of effects on material thyroid hormones, and
did not provide a compelling argument that lower reserves or shorter retention in the mother affects
the neonate in any way. Just below this in the recommendation it is not clear if the SAB is advising EPA to consider lower reserves and shorter half lives in fetuses and infants (see lines 16-17) or in pregnant adults (in comparison with non-pregnant adults, lines 30-31). This should be made explicit. Which
'sensitive life stages' are being referred to in lines 33-34? The final line, 36, of this recommendation "Additionally this issue may be studied in animals using appropriate experimental design." is undeniably true, but it is not a recommendation. Is the SAB recommending such experiments be undertaken and if so, how would results from these studies assist the EPA in determining how to take into account differences in different life stages?

Section 3.1.5 seems to repeat material from 3.1.1. Section 3.1.5 is titled "intrauterine exposure to perchlorate and thyroid status impact in fetuses;" however, the material is more general, focusing on pathways through which altered thyroid function affects pregnant women and their children. This content seems out of place. In this section I expected to read about studies specific to perchlorate levels in pregnant women, but this material appears later in 3.3.1.

Neither the EPA report nor the SAB report spend much time on the potential for mixture effects on thyroid function. See for example: Steinmaus et al, 2013. This is discussed in Appendix B as one of the challenges to use of the new epidemiology data. A recommendation

appears on page 24 related to co- exposures; however, I would recommend the SAB provide some guidance regarding the analysis of mixtures with similar MOAs. Page 18, lines 6-8 suggest other NIS inhibitors could be incorporated into the model but are currently addressed only qualitatively. The SAB should provide a recommendation on this topic. Can the PBPK/PD-IUI model be relied on for development of a MCLG with other NIS inhibitors considered only qualitatively?

It is not clear why in responding to charge question 3, which specifically asks about the use of the post- NRC epidemiology work, that the SAB chose to relegate the analysis of this literature to the appendix (B). Section 3.3.2 is quite short, and makes conclusions based on the more in depth analysis discussed in Appendix B. It would make more sense for this material to be in the body of the report.

Section 3.3.3 warns about pooling of epidemiology data, without providing guidance on how the EPA can undertake post-hoc pooled analysis. What specific sources of heterogeneity are observed in the studies that should be considered carefully in a pooled analysis?

Page 19, lines 38-39 are unclear. "data that inform the exposure modeling appear somewhat variable in extent across the lifestages" Does this mean the amount of data available is variable or the numerical values of the data are variable? If the former, how does this affect the modeling (it is a limitation, but what effect does it have?). If the latter, wouldn't we expect the data from different life stages to be different? Why is this relevant as a model limitation?

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The primary conclusion that sensitive life stage analysis is critical for a MCLG for perchlorate is well supported by the draft report. There is little doubt that the mode of action for potential perchlorate effects will have differential impact on humans in different life stages.

The shift in focus from hypothyroid to hypothyroxinemic in pregnant or lactating women as an indicator of risk to the fetus and breastfed neonate is well –supported and important. Low T4 (hypothyroxinemia) even in the absence of abnormal TSH associated with hypothyroidism has recently been reported to increase fetal risk for negative neurological outcomes. Given the confusion over these terms and their implications, it would be good for the report to include a bit more on the actual definitions of these two states relative to the euthyroid state and how these definitions change in different life stages (e.g., the reference range for normal TSH is different in pregnant and non-pregnant women).

I question the specific identification of life stages for the adult as relevant. There is no indication that the adult pregnant or lactating woman is at risk. The woman is effectively the pathway for exposure to the fetus and breastfed neonate. While this is likely clear to the reader since the MOA for perchlorate is discussed so many times in so many places, since life stage is

the issue, it should be clear in the document that pregnancy and lactation do not increase the risk to the adult woman. Any reduction in T4 associated with perchlorate exposure to the woman will likely have transient and reversible neurological effect. The redefinition of the sensitive population from 'fetuses of pregnant women" to 'pregnant and lactating women and infants" should be explained more fully. The sensitive population is usually defined as the population with a higher risk rather than the population whose exposure will lead to the highest risk for another population. The reframing suggested in the report seems reasonable, but should be better explained since the delineation of sensitive subpopulation related to perchlorate from the NRC report has been the norm for some time.

The very strong statement on page 20, line 34 "the current body of epidemiologic evidence cannot provide validation of a safe level of perchlorate in drinking water" requires further support. The charge question asked only about post-NRC epidemiology data, not the full body of epi evidence. Did the SAB committee review all the epidemiological data including in the NRC review as well as post-NRC data? The NRC report provided guidance on a NOEL and a RfD, which suggests the epi data considered by the NRC was sufficient to propose a safe level, if perhaps not sufficient to validate that level. I would suggest revision of this sentence to capture the nuance that the epi data is not without use in determining a safe level, even if it is insufficient to be used for validation. This is particularly important since throughout the earlier part of the report, the pathway from perchlorate exposure to negative outcomes in pregnancy is discussed repeatedly. Later in this section the report indicates the epidemiological studies since the 2005 NRC report are insufficient to support a derived MCLG (page 23, lines 18-19). This is a more qualified conclusion and better supported by the analysis completed by the SAB. This is further supported by the SAB report page 25, lines 31-33, and page 26, lines 18-21, where the need to consider the full available literature in development of the MCLG is discussed. Further, the Executive Summary states "there is sufficient information to derive an MCLG for perchlorate" I would recommend consistency throughout the report and executive summary on this important conclusion.

Angela M. Leung, Lewis E. Braverman, Xuemei He, Kristin E. Schuller, Alexandra Roussilhes, Katherine A. Jahreis, and Elizabeth N. Pearce. Environmental Perchlorate and Thiocyanate Exposures and Infant Serum Thyroid Function. Thyroid. September 2012, 22(9): 938-943. doi:10.1089/thy.2012.0058.

Craig Steinmaus, Mark D. Miller, Laura Cushing, Benjamin C. Blout, Allan H Smith. Combined effects of perchlorate, thiocanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-2008, Environmental Research. March 2013, in press corrected proof, http://dx.doi.org/10.1016/j.envres.2013.01.005

Comments from Dr. John Vena

1) Were the charge questions to the committee adequately addressed?

The answers to each of the charge questions were well organized. For each answer background material is summarized followed by comprehensive answers to the charge question followed by well articulated recommendations.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No errors or omissions or issues that were not adequately addressed.

3) Is the draft report clear and logical?

The cover letter is well written and very clear on advice to EPA on approaches. The executive summary is excellent. I recommend that the specific recommendations noted in the summary also be listed at the end of the executive summary.

I support the SAB recommendation that hypothyroxinemia is a more appropriate indicator than hypothyroidism. They basis of that recommendation is well described. I also support the novel approach recommended by the SAB to use PBPK/PD-IUI modeling to derive the MCLD.

The SAB provides a superb rationale for considering the life stages approach.

I carefully read section 3.3 that reviews the epidemiologic studies done since 2005 and the supporting narrative in Appendix B. The SAB panel has done well in putting the epidemiologic evidence into perspective. Appendix B is excellent starting with a description of the ideal study followed by identification and description of the 13 relevant studies since 2005 followed by systematic critique.

The steps for the MOA modeling approach are very clear and Figure 2 is excellent.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. R. Thomas Zoeller

The following comments are provided in response to the March 29, 2013 memo by DFO Dr. Angela Nugent concerning SAB review of *SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate*. This memo asked contributing SAB members to specifically address the four quality review questions from the vantage point of our own expertise. These questions are:

1. Were the charge questions to the committee adequately addressed?
2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report;
3. Is the draft report clear and logical; and
4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report.

In general, the SAB committee has generated an extremely impressive report that addresses the complexity of the issues facing the Agency in a clear and scholarly way. This undoubtedly reflects the scientific acumen and professionalism of the scientists assembled for this report as well as the leadership of the chair. I will address these four charge questions for the quality review within the context of the Agency questions to the Committee.

Agency Questions for the Committee

In general, all of the charge questions were addressed clearly and were well delineated in the report. These charge questions are complex because of the complexity of thyroid hormone action on development and adult physiology, and because of the complexity of the literature focused on the health effects of perchlorate exposure. Accordingly, the Agency developed 4 sets of charge questions to direct the attention and advice of the SAB, as follows:

Issue I – Sensitive Life Stages. The Agency posits that there are currently no data to directly link perchlorate to neurobehavioral effects in [human] infants and children. How should EPA consider the following life stage factors in deriving an MCLG?

Life stage specific differences in body weight and food and drinking water intake
Differences in greater severity and permenance of potential adverse effects in neonates, infants and young children compared to adults
Shorter half-life and lower reserves for thyroid hormone in infants compared to adults
Intrauterine exposure to perchlorate and impact on thyroid status in fetuses.

In general, the SAB addressed these questions clearly, recommending that life stage be incorporated into the development of an MCLG. Moreover, the SAB recommended that the fetus, the neonate and infant be identified as the most sensitive life stages. Further, the SAB recommends using the MOA for perchlorate action articulated in the 2005 NRC report on perchlorate but to use "hypothyroxinemia" as the first adverse effect. The SAB clearly develops the background information supporting this recommendation and clearly articulates why the neonate and infant should be included as protected life stages. In short, the argument is that while little to know information is available to directly link perchlorate to cognitive and neurobehavioral deficits in this population, there is simply more scientific evidence – with high quality dose-response relationships – to link thyroid hormone levels to brain development in this population than in any other subgroup of the population. Because the MOA of perchlorate is known, it is reasonable to infer relationships between perchlorate exposure and adverse effects on brain development. The SAB makes this point very clear.

However, there are two issues that the committee may consider making more clear. First is the issue that T_4 has a shorter half-life in neonates than in adults, and that there are lower reserves of T_4 in the neonatal thyroid gland. Although there are few studies that characterize these issues in humans, the three available studies all conclude that

neonates need all the thyroid hormone they produce. That is, there is essentially no stored T_4 from which they can draw if thyroid hormone synthesis is impaired by perchlorate (or any other chemical interference) and serum T_4 half-life is only 3 days. This is fundamentally different from the adult (from which the RAIU data are derived) in which there are thought to be months-worth of thyroid hormone stored in the gland and the serum half-life of T_4 is 7-10 days. The implication of these details to development of a MCLG may clarify the importance of these issues.

Second is the issue of "compensation". While this issue is not directly requested in the charge questions, it is an issue for which there is evidence that it changes over various life stages. In addition, the 2005 NRC report employed this concept multiple times, pointing out the resiliency of the developing brain to perturbations in thyroid hormone availability, although there was not a single scientific reference to support this concept. In short, "compensation" refers to the presumed ability of animals and humans to mount adaptive responses to low (or high) levels of thyroid hormone such that the potential impacts of thyroid hormone insufficiency (or excess) can be ameliorated. These responses would include changes in serum TSH, changes in the expression of transporters or deiodinases that control delivery of thyroid hormone to the right place at the right time. This concept of "compensation" directly affects the way incomplete datasets are interpreted. Specifically, when the data set includes chemical exposure and thyroid hormone levels, but no measures of thyroid hormone action, then the concept of "compensation" can be employed to interpret the "toxicological relevance" of the changes. The observation that small changes in thyroid hormone levels affect brain development in both animals and humans does not support the concept of compensation. Moreover, a recent study in animals found no evidence for compensation in a neonatal rodent (J Neuroendocrinol 22:153-165).

Issue II – Physiologically-Based Pharmacokinetic Evidence. The Agency asks how they should consider PBPK modeling to derive an MCLG for perchlorate and to identify the strengths and limitations of the two PBPK model results described in this effort.

The SAB did an excellent job in addressing this issue and provide clear and detailed recommendations about the models employed by the Agency and how they can employ existing data to improve their analysis.

Issue III – Epidemiological Evidence. The Agency asks how they should consider the post-NRC epidemiology data in deriving an MCLG.

The SAB did a very clear and thorough job in advising the Agency concerning the use of the post-2005 epidemiology data. Appendix B is particularly important in this regard and they provide very clear and thorough analysis of the information. However, the SAB may consider including a discussion of the variability of the set-point around which thyroid hormone is regulated in individuals and its relationship to population reference ranges. The first issue is exemplified by the work of Andersen et al. (J Clin Endocrinol Metab 87:1068-1072). Specifically, they show that the normal variability in thyroid hormone levels in an individual is only a small proportion of the variability identified in a larger group (or the population reference range, see Figure 1). Recognizing the importance of this variability, Andersen et al also calculated the number of tests required to establish the set-point for an individual (see Table).

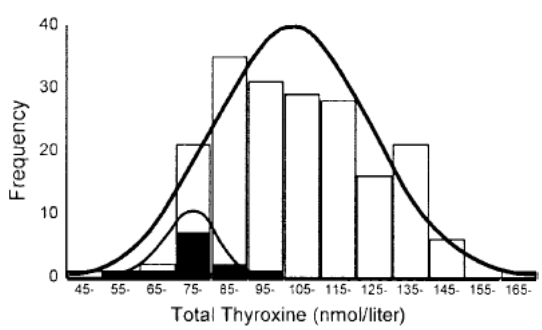

FIG. 2. The distribution of 12 monthly measurements of total T_4 in 15 healthy men (□) and in one individual, number 11 (■). The distribution in one individual is about half the width of the distribution in the group.

TABLE 2. Number of tests required to describe the homeostatic set point in an individual

	Precision of set point		
	5%	10%	25%
TSH	85	25	5
TT_3	25	5	1
TT_4	25	5	1
FT_I	25	5	1

Calculated from: $n = (Z \times CV_{analytical}^2 + CV_{intraindividual}^2)^{1/2}/D)^2$ where: D is percent closeness to the homeostatic set point, Z is the number of standard deviations required for a confidence interval (*i.e.* 1.96 for 95%), n is the number of specimens.

This is important because this variability needs to be formally addressed in epidemiological studies when study size or number of measurements is being considered. In a case like this occurs in which there is predictable variation, it needs to be incorporated into study design for power considerations. Another study focusing on mono- and di-zygotic twins, concluded that genetics plays a particularly important role in establishing this set-point (Clin Endocrinol (Oxf) 68:652-659.); therefore, it is important to recognize that there may be even more variability in a population that is highly heterogeneous in terms of race and ethnicity.

Issue IV – Integration of Information – The Agency asked how they can best use the total body of information to derive a health protective MCLG, while considering the results of epidemiology and biomonitoring data in establishing bounds on potential values? They also asked for advice to guide them in using the available data to estimate reductions in adverse health effects (i.e., dose response) that are likely to result from reducing perchlorate levels in drinking water.

The Agency addressed this issue in a section designated as such. This was a clear and cogent section based on the background information they presented. However, the second part of this question did not seem thoroughly articulated. Specifically, the document indicates that the epidemiological data presented to the committee did not provide sufficient information to develop a dose-response relationship that would allow one to calculate the reduction in adverse health effects. This suggested that there are more epidemiological data available, they just weren't made available to the committee. Is this correct?