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David Allen, Ph.D.
Chair
US EPA Science Advisory Board
200 E Dean Keeton St. Stop C0400
Austin, TX 78712-1589

RE: Comments on the report *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate*

Dear Dr. Allen:

My colleagues at Intertox and I appreciate the opportunity to respond to the recent draft document *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate* (Draft Report). We have been retained by the Perchlorate Study Group (PSG)[1] to conduct an independent review of the recent Science Advisory Board (SAB) draft document. Intertox has studied the toxicology and pharmacology of perchlorate for over 15 years. Our firm has made a number of scientific contributions to the database for this chemical by providing scientific reviews and comments, conducting research, and assisting government agencies in a thorough scientific evaluation of perchlorate exposure. The goal of our work is to identify the health risks associated with perchlorate in drinking water and to ensure that regulatory standards for perchlorate in drinking water are protective of the most sensitive population.

We have had a productive dialogue with the *ad hoc* SAB and would like to share our previous communications with the Charter SAB (see Appendix). Upon reading this new draft document we recommend that the Charter SAB focus on key issues as it provides a quality review of the current Draft Report. The current version is the third draft prepared by the SAB in response to the United States Environmental Protection Agency (US EPA) White Paper titled *Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate* (White Paper).

We encourage you to evaluate the previous drafts and deliberations, which contributed to the recommendations set forth in the current version. In addition, we recommend that you consider the following four scientific issues associated with the current draft:

- The final report should not state that it supplants the National Academy of Sciences, National Research Council's (NRC's) determination, in its exhaustive 2005 review of the relevant perchlorate science, that the pregnant woman and her fetus are the most sensitive population. We note that the Panel has suggested that the hypothyroxinemic pregnant woman and her fetus, as well as the infant, are the most sensitive subpopulations.

[1] The PSG comprises Aerojet General Corporation, American Pacific Corporation, Alliant Techsystems Inc., and Lockheed Martin Corporation.

- The final report should include a clear, thorough and complete description of how US EPA should use the Physiologically-Based Pharmacokinetic Pharmacodynamic Model (PBPK/PD) to properly assess the potential adverse effects associated with exposure to perchlorate in drinking water at sensitive life stages.
- The final report should include a detailed evaluation of the dose-response information essential to the identification of those levels of perchlorate that produce key biological effects.
- If the infant is to be identified as the most sensitive subpopulation, the document must provide clear science-based support, with consideration of dose-response, for its discussion of the most sensitive population.

Brief background

Perchlorate's mechanism of action is well-understood. It is uncommon to find such a robust database for an environmental chemical. Perchlorate has been researched for over 60 years as a pharmaceutical agent and as a naturally-occurring and man-made environmental chemical. In the late 1990s and early 2000s, thirteen animal studies and five human clinical studies were conducted to fill important data gaps. The health effects of perchlorate have been evaluated by several authoritative bodies, including the NRC, US EPA, and the Agency for Toxic Substances and Disease Registry (ATSDR).

The NRC recommended, and US EPA adopted, a Reference Dose (RfD) based on a **No Observable Effect Level** (NOEL), as opposed to the No Observable Adverse Effect Level (NOAEL) for perchlorate, based on the clinical study conducted by Greer et al. (2002). The NOEL is based on the dose at which there is no change in inhibition of iodide uptake, which itself is nonadverse and occurs several biochemical steps before the first adverse effect, hypothyroidism. The NRC stated with emphasis:

> Inhibition of iodide uptake by the thyroid clearly is not an adverse effect; however, if it does not occur, there is no progression to adverse health effects.

The NRC considered the NOEL to be a transparent and conservative point of departure for risk assessment, yet also chose to apply an uncertainty factor of 10 to account for sensitive subpopulations, which included **pregnant women, fetuses, infants, and people with existing thyroid problems.** Thus, the sensitive populations that the SAB now requires to be considered **have been evaluated**. There is no new, reliable, scientific information that has been published that supports any changes to the work of the NRC and its conclusion that a RfD drinking water equivalent level of 24.5 ppb is protective of even the most sensitive populations.

Issues to focus upon

<u>Change in NRC recommendation of the most sensitive subpopulation:</u>

<u>Issue</u>: The SAB has chosen to "replace [as the most sensitive subpopulation] 'the fetuses of pregnant women who might have hypothyroidism or iodide deficiency' as defined by the NRC" with the hypothyroxinemic pregnant woman and her fetus and the breast-fed or formula-fed infant. The SAB Panel had neither the resources, nor the required time, nor the expertise needed to make a thorough assessment of sensitive populations equivalent to that provided by the NRC; additionally, no evidence has been presented that infants are equally as sensitive as fetuses.

The NRC panel was "selected for their expertise in pediatrics; endocrinology; pediatric endocrinology; thyroid endocrinology, physiology, and carcinogenesis; immunology; veterinary pathology; animal toxicology; neurotoxicology; developmental toxicology; physiologically-based pharmacokinetic modeling; epidemiology; biostatistics; and risk assessment" and took over two years to complete their extensive evaluation of the database. The SAB Panel had only a few months for its review, and lacked the same expertise as the NRC (e.g. lack of a thyroid endocrinologist). In addition the SAB did not have equivalent access to scientific material, had a much narrower scope of review regarding the scientific database, and had a much more limited set of charge questions. The SAB Panel's review simply cannot hold weight equivalent to that carried by the NRC's process and conclusions.

Physiologically-Based Pharmacokinetic Model

Issue: It is not clear how the SAB recommends that US EPA use the PBPK/PD modeling. The SAB report should be very clear on how the model should be developed and used, as members of the panel have specific expertise on the subject.

We agree with the SAB Draft Report on a key issue: the use of the PBPK/PD modeling is a superior and more scientific approach for deriving the Maximum Contaminant Level Goal (MCLG) than using US EPA's traditional algebraic approach for calculating the MCLG. PBPK/PD provides a robust scientific tool that can address questions related to changes in physiological function in response to exposure, such as changes in iodine uptake inhibition (IUI) or thyroid hormones. We have provided comments on this issue, including, for example, that policy should not be a component of the PBPK/PD model algorithms. We provide links to our scientific comments in the Appendix to this letter. We also agree with the SAB that it is in US EPA's best interest to extend the PBPK/PD model to describe changes in thyroid hormone levels and downstream effects, as the current US EPA model generates data only on IUI, an effect that is mechanistically upstream from any adverse effects.

The best use of the model would be for examining the doses of perchlorate that would lead to adverse thyroid changes at different life stages. The SAB should recommend that US EPA avoid selectively using the model. In the White Paper, US EPA uses the PBPK/PD model to demonstrate that infants are more sensitive than the fetus; however, US EPA fails to address the fact that the PBPK/PD model predicts a very low level of IUI change (less than 3.4%[2]). This small change in a non-adverse effect is far removed from any potential adverse effect. The White Paper also suggests that, based on the PBPK/PD model, an "uncertainty factor [of 3] may not account for the full differences in perchlorate pharmacokinetics…" This conclusion is not scientifically valid and amounts to a selective application of data that should not be permitted.

Dose not considered

Issue: Dose was not assessed or considered in this draft document. Dose-response relationship is a fundamental concept in both toxicology and risk assessment, and is necessary for this assessment. The SAB document should be required to address dose-response in all aspects of its evaluation.

Given that most risk assessments are based on either a NOAEL or LOAEL, using a NOEL provides superior opportunity to address risk with a scientific level of certainty, without

[2] Corresponding to a 7-day old, bottle-fed infant drinking water containing perchlorate at 24.5 ppb and the contribution of 0.1 µg/kg-d from food (Table A-4, US EPA White Paper).

recourse to the use of inexact uncertainty factors. The NRC concluded that there could be abnormal fetal and child growth and development with maternal hypothyroidism, but this could occur only with a reduction in iodine uptake to the thyroid of at least 75% for months or longer. They also concluded that the dose required to cause hypothyroidism in adults would probably be more than 0.40 mg/kg –d. In contrast, the NOEL reported in Greer et al. (2002) is 0.007 mg/kg-d, 57 times lower than the NOAEL. The RfD is 0.0007 mg/kg-d, 570 times lower than the NOAEL. As an additional example, when perchlorate was used pharmaceutically, it was routinely given to pregnant women with doses of approximately 1 g/d with no reports of long-term adverse effect in infants (Crooks and Wayne, 1960).[3]

The Draft Report discusses studies of neurodevelopmental effects of iodine deficiency or thyroid hormone deficiency and makes clear that there are no studies that demonstrate that perchlorate causes or exacerbates these effects. Clearly insufficient iodine or thyroid hormone deficiency can cause detrimental effect on neurodevelopment; however, we stress that this does not occur at environmentally-relevant doses of perchlorate, or due to other more common and more abundant IUI inhibitors at environmental levels. Nitrate and thiocyanate are both found in a normal diet in quantities that dwarf that of perchlorate. Even when considering these chemicals in perchlorate equivalence, their impact on total change in IUI is greater than 98% while that of perchlorate is less than 2%. If one were to believe that there currently exists an unmitigated public health issue due to goitrogenic compounds in food and drinking water, it is clear that deriving an MCLG for perchlorate in isolation will not provide a solution.

Scientific Support

Issue: The questions that the Charter SAB must consider when evaluating the Draft Report regards whether the conclusions or recommendations of the Draft Report are supported by the body of the Draft Report and whether there are technical errors or omissions. The SAB should be given ample time, opportunity, and scientific expertise to make this determination.

The Agency's White Paper presents no scientific justification that the infant is more sensitive than, or as equally sensitive as, the fetus. We have requested that US EPA provide this information. There are clear means to scientifically address this issue, such as showing a slower clearance rate, a difference in the efficiency of the sodium iodide symporter, or a difference in metabolism (perchlorate is not known to be metabolized). The fact that body weight is different or that children might have greater intake is not sufficient justification to adjust the risk assessment paradigm. Similarly, there is no scientific support for using the PBPK model, which presents a non-adverse precursor effect (IUI), as evidence of greater sensitivity to an adverse effect.

The Lead Reviewers have a critical task with important ramifications in evaluating this document. We suggest that you ask rigorous science-based questions and reflect as to whether the Panel was given adequate resources and time to assess the science and to make the determinations included in the Draft Report. The Lead Reviewers should request that the SAB Draft Report undergo further assessment that would include sufficient time and resources to publish a scientifically rigorous assessment.

[3] Crooks and Wayne (1960) report on the treatment with potassium perchlorate of 12 pregnant women who developed hyperthyroidism during pregnancy. The authors report that "one of the infants had a very slight enlargement of the thyroid gland which disappeared within 6 weeks. The remainder showed no abnormality of any kind."

Conclusion

We thank you and your colleagues on the SAB as well as at US EPA for a continued focus on key scientific matters regarding perchlorate. We appreciate your consideration of our comments. The following attachment includes short descriptions and links to our previous comments for reference. We would be happy to further this discussion, and are available for questions.

Sincerely,

INTERTOX, INC.

Richard C. Pleus, Ph.D.
Director / Toxicologist

Appendix

List of Materials Provided by Intertox or PSG to the *ad hoc* SAB

Critical Review of the US EPA White Paper. Intertox noticed that US EPA did not include the entire database of studies regarding perchlorate, and instead focused on a limited set of studies published after 2005. These selected studies were used to justify the use of life stages to calculate an MCLG, using the algebraic approach and the PBPK model to suggest that infants are more sensitive than fetuses. Intertox recommended that US EPA evaluate the entire database of studies dating back over 60 years and evaluating the weight of scientific evidence. Intertox also noted that the US EPA model had embedded policy decisions in its PBPK model. Finally, Intertox evaluated the strengths and limitations of the selected studies that US EPA evaluated.

Presentation by Dr. Richard Pleus at the July 18-19 SAB meeting.

Summary of Key Scientific Information in Response to the July 18-19 Meeting. Intertox noted during the meeting on July 18-19 that several of the SAB members were asking questions or suggesting that research be performed that was already available in the database. Realizing that the SAB was given limited time, Intertox provided this information.

Letter from Intertox to the SAB expressing concern regarding the limited resources they were given to respond to the charge questions.

Response of Dr. Pleus to specific questions from SAB Panel members.

Letter from Intertox to the SAB following the September 25 teleconference. Response to SAB's request to provide examples of policy statements in the SAB draft and also in the US EPA PBPK model.

Letter from PSG to the SAB providing comments to the September 5 Draft Report.

Bruce et al. (2013). Two earlier studies were used by US EPA to demonstrate an association between urinary perchlorate and reduced thyroid function in women with a spot-urine iodine measure less than 100 µg/L with environmental exposure to perchlorate using NHANES 2001-2002. These two studies were contrary to the weight of evidence, but were cited nonetheless. Since this time, a revised NHANES 2001-2002 dataset has been released reanalyzing the previous two measures (total T4 and TSH) and expanding the suite of measures of thyroid function. This new dataset was reanalyzed and there was no evidence of reduced thyroid function in this or any other group.

Letter from Intertox to the SAB providing comments to the November 9 Draft Report.