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Stephen M. Roberts, Ph.D.
Chair, Science Advisory Board Perchlorate Advisory Panel
c/o Mr. Tom Carpenter, US EPA Designated Federal Officer
US Environmental Protection Agency
Washington, D.C.
Delivered via email

RE FOLLOW UP TO US EPA'S SAB TELECONFERENCE "Perchlorate Advisory Panel
Teleconference —Discussion of Draft Advisory Report On Maximum Contaminant Level
Goal Approaches" HELD ON SEPTEMBER 25, 2012

Dear Dr. Roberts:

I appreciate the ongoing dialog I have been able to have with you and the SAB through public presentations at the meeting in Washington, D.C (July 18-19, 2012) and the teleconference and through submittals. Thoughtfulness, transparency, and scientific rigor are essential in this MCLG process and the exchange of scientific information is part of this process. During the teleconference on September 25, 2012, you and Dr. Anderson requested some information regarding policy issues for two areas the SAB is reviewing. You requested that I provide the SAB with examples of

- policy statements contained in the Draft SAB document, and
- policy components in the US EPA PBPK model.

In response to these requests, I am happy to provide the following information in attached appendices. These are provided as brief examples to support our point.

- Appendix A provides examples of statements in the SAB draft.
- Appendix B provides examples of statements that could affect the outcome of the SAB deliberations that need scientific support. I provided several examples during the teleconference.
- Appendix C provides examples of policy embedded in the US EPA PBPK model.
- Regarding the unanswered questions, these are covered in previous documents that I have provided the SAB and can be found [here](#).

Again, I appreciate the opportunity to submit information to you, your committee, and the US EPA on this matter. I would be happy to address any questions you might have.

Sincerely,
INTERTOX, INC.

Richard C. Pleus, Ph.D.
Managing Director and Toxicologist

October 3, 2012

cc:

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Appendix A Policy in SAB Draft

In general, science policy occurs when an authoritative body decides on how to proceed given scientific information. US EPA states “Policy documents represent EPA’s official interpretation or view of specific issues.”¹ Furthermore, US EPA comments on the application of science in policy decisions:

Science does not drive EPA's policy and regulatory decisions, but rather, along with other relevant factors, informs and supports those decisions. Implementation costs and technological feasibility, local autonomy versus federal control, and justice and equity--all of which impact our quality of life and standard of living--are among the considerations that need to be factored into EPA's decisions without compromising scientific integrity, the Agency's mission, or statutory mandates. The impacts or limitations of these non-science factors, as well as the current state-of-the-science, will influence how scientific considerations are brought to bear on a particular environmental problem facing the Agency.²

US EPA did not provide the SAB with guidelines related to science policy, and the Committee may want to request guidance as the final draft of your report is produced. The Agency’s Information Data Quality Act (IDQA) also provides guidelines useful in determining the nature, amount, and quality of the data needed to support not only scientific assessments but also science-based judgments, such as development of policy. Henry and Conrad (2008) gives a brief survey:

As a general matter, information must be accurate, reliable, and unbiased. Scientific information must be generated using sound research methods. The sources of the information must be disclosed and data should be documented. Scientific information must be accompanied by supporting data and models. “Influential” scientific information must be sufficiently transparent to be reproduced subject to several caveats. (“Influential” information is that which an agency “reasonably can determine will have or does have a clear and substantial impact on important public policies or private sector decisions.”) Influential information regarding risks to health, safety, or the environment must also be based on “the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and . . . data collected by accepted methods or best available methods,” and must disclose significant uncertainties and relevant peer-reviewed studies.³

Our concern is that there has not been an acceptable review of the full database of literature on perchlorate in a manner that would comply with the scientific information requirements outlined by the IDQA. A decision by the Agency to move forward based on consideration of a limited data set is neither sufficient nor transparent. We provide some examples.

¹ <http://www.epa.gov/lawsregs/policy/>

² <http://www.epa.gov/osp/science.htm>

³ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2199282/>

Quote from <i>Science Advisory Board (SAB) Draft Advisory Report (September 5, 2012)</i>	Why is it policy?
<p>...that any observed changes in brain development caused by perchlorate exposure should be considered adverse until otherwise shown to be non-adverse due to the difficulty in correlating changes in brain development (e.g. altered expression patterns of TH-regulated brain genes) with functional effects. (p. 8)</p>	<p>This statement is policy as it directs a general interpretation of “changes” without providing scientific support or acknowledging key data deficiencies that provide a rationale for the policy. Some members of the SAB may have looked at only a portion of the literature on perchlorate and not reviewed studies or authoritative documents addressing the broader literature on brain development. For example, the SAB did not conduct an analysis of the plentiful animal data for other thyroidal agents that demonstrate the degree of thyroid hormone change needed to cause an adverse effect.</p>
<p>The fetus and infant are more susceptible to effects from perchlorate exposure than the adult (as above) is. (p. 11)</p>	<p>This statement is policy as it directs a general interpretation of the relative sensitivity of life stages without providing scientific support or acknowledging key data deficiencies that provide a rationale for the policy. Furthermore, US EPA asked the SAB to evaluate the scientific merit of the assertion that in all cases the fetus and infant are more susceptible than the adult via Sensitive Life Stages. However, this conclusion would require review of the pharmacokinetic and pharmacodynamics processes for many types of chemical agents (in addition to perchlorate) which the SAB has not done. Our own assessment has demonstrated that young children and neonates have clearance rates that are similar to or greater than adults (Appendix A, Supplemental Tables 1 and 2).</p>
<p>Hypothyroxinemic pregnant women should be considered the sensitive life stage; this would replace pregnant women with clinical hypothyroidism as the sensitive life stage as defined by the NRC (2005). (p. 22)</p>	<p>This statement is policy as it directs a general interpretation of the sensitivity of pregnant women without providing scientific support or acknowledging key data deficiencies that provide a rationale for the policy. In contrast to NRC (2005), which conducted a full evaluation of literature up to 2005 and made a scientific determination, this statement makes a scientific judgment about an issue without sufficient scientific information.</p>

Appendix B Statements that lack scientific support in SAB Draft

Quote from <i>Science Advisory Board (SAB) Draft Advisory Report (September 5, 2012)</i>	Comment
<p>Perchlorate inhibits iodine uptake and therefore interferes with TH production. Perchlorate acts by specifically inhibiting NIS-mediated transport of iodide into the thyroid, as well as in the placenta and lactating breast. (p. 7)</p>	<p>This statement concludes that perchlorate interferes with TH production, but excludes discussion of dose, duration, or compensation. In the absence of this information, the statement is misleading and makes a determination regarding perchlorate health effects without scientific support.</p>
<p>The SAB finds that existing data are inadequate for quantitatively estimating reduction in adverse health effects realized in regulating perchlorate in drinking water. Specifically, the available data are not adequate to support fully quantitative dose-response modeling and related adverse health effects reduction analyses. (p. 25)</p>	<p>The SAB did not conduct an assessment to determine this. The SAB did not review the entire database to allow such a statement to be made. No dose response assessment was conducted. There are sufficient data to make this determination but the SAB has not reviewed such data.</p>
<p>The SAB recognizes a range of neurodevelopmental impairments in the infant as the “adverse effects.” However, measurements relevant to these adverse effects may range from iodine deficiency, hypothyroxinemia, changes in expression of genes involved in brain development and function, neuropsychology, and impaired behavior, learning and memory, among others (Rovet and Willoughby 2010); (p. 25)</p>	<p>No results from studies with perchlorate are reported or referenced. No studies from the literature where animals are given other thyroidal agents and thyroid hormone changes are assessed were reported. These “adverse effects” have not been defined or been shown to be relevant to perchlorate exposure at environmental levels.</p>

Appendix C Examples of Policy Embedded in the EPA PBPK Model

Further information can be found in the [Intertox assessment of the EPA White Paper](#).

Aspect of US EPA PBPK/PD Model	Comment
<p>Values were chosen without clear scientific support. The lowest value was chosen (out of three peer-reviewed studies) to represent the urinary clearance of pregnant women. US EPA (2009) declares that all three clearance values considered had a similar quality and amount of supporting data; in fact, this cannot be true based on the information presented. The value chosen was of low scientific quality (it is not supported by either source EPA cites as its primary basis, <i>i.e.</i>, Greer <i>et al.</i> (2002) or Tellez <i>et al.</i> (2005)) and higher values are better supported by the scientific literature, as discussed below.</p>	<p>When values are selected for incorporation in the model, a consistent rationale should be applied in choosing these values.</p>
<p>Values were chosen from inconsistent points in their distributions. US EPA (2009) states that the urinary clearance value was selected to “represent the best or most likely (central) estimate for an average individual within the population.” Selecting the <i>lowest</i> urinary excretion value—one that produces the highest estimate of RAIU inhibition—is not the “average.”</p>	<p>When conducting calculations to reflect exposure within a population, each parameter can have a range of possible values. In order for PBPK model output to be meaningful, the basis for selection of specific values within the range of possible values should be described and the relationship to the overall distribution for that parameter should be characterized (<i>e.g.</i>, lower-bound, average, median, upper-bound).</p>