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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: CONCERN REGARDING THE FUNDAMENTAL SCIENCE OF PERCHLORATE

Dear Dr. Roberts:

Intertox has been involved in the review and development of the science of perchlorate health effects on behalf of the Perchlorate Study Group (PSG) since 1999. The PSG collaborated with US EPA in conducting many animal studies that investigated the effects of perchlorate on a number of different body systems. Intertox has reviewed hundreds of scientific studies and used this background along with input from US EPA (and DOD) to develop the protocol for the [Greer et al. \(2002\)](#) study, of which we are coauthors. As you are likely aware, that study was chosen by the National Academies of Science National Research Council (NRC) and many state agencies as the point of departure for setting an acceptable level of exposure to perchlorate. Based on these reviews, Intertox has also prepared many independent and publically available assessments of the scientific database. It is with this history that I write this letter.

I attended the perchlorate Science Advisory Board (SAB) meeting on July 18th and 19th, and during the public comments I raised two important concerns, specifically,

- 1. The narrow scope of the research the SAB was charged with considering, as compared to the breadth of the scientific database on perchlorate, and**
- 2. The short timeframe in which you and the SAB must complete your scientific review.**

These matters are of such importance to the SAB's work that I am prompted to reiterate these concerns in writing, in the hope you will share this with your fellow panelists and take the necessary steps to ensure the SAB's judgments are based on the best available science as required by the Safe Drinking Water Act.

THE SCOPE OF THE CHARGE IS LIMITED: BY OMITTING MUCH OF THE SCIENTIFIC DATABASE ON PERCHLORATE, THE CHARGE LEAVES THE SAB WITH AN INCOMPLETE ASSESSMENT ON PERCHLORATE

I remain concerned that the scope of the work the SAB was asked to review omits a

significant portion of the body of scientific information available to help inform the SAB members. The US EPA-prepared White Paper provided to the SAB:

... presents scientific information published **since** [emphasis added] the National Research Council (NRC) released their 2005 Report... The purpose of this white paper is to seek guidance from the Science Advisory Board (SAB) on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data **since** [emphasis added] the NRC Report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate (p. 4).

Given that the scientific database for perchlorate spans more than 60 years, the information the SAB has been asked to consider represents only the tip of a very substantial iceberg.

PROVIDING THE SAB WITH AUTHORITATIVE SCIENTIFIC DOCUMENTS REPRESENTATIVE OF THE COMPLETE SCIENTIFIC DATABASE WOULD HAVE PROVIDED IMPORTANT INFORMATION

The extensive knowledge regarding perchlorate health effects has been rigorously evaluated and used by several independent, authoritative bodies as the bases for perchlorate risk assessments. New data should be evaluated in context, with the benefit of the full body of literature rather than in isolation. In particular, the SAB would have benefitted by review of one or more of the following four authoritative reviews:

A. [NRC \(2005\). Health Implications of Perchlorate Ingestion.](#)

The SAB would have greatly benefitted from having a member who was also on the 2005 NRC committee or, alternatively, to have a NRC committee member present to advise the SAB as needed during its deliberations, and conclusions. A minimum recommendation is for the SAB to carefully review the NRC document prior to the next SAB meeting.

Barring that, NRC's *Health Implications of Perchlorate Ingestion* (2005) report contains vital conclusions for the SAB that were not adequately covered in the US EPA White Paper. Specific points are summarized below, with embedded links to the direct text in the report:

- 1) [Iodide uptake inhibition \(IUI\) is the only consistently demonstrated biochemical effect of perchlorate; it has been unequivocally demonstrated in humans exposed to perchlorate, and it is the key event that precedes all thyroid-mediated effects of perchlorate exposure.](#)
- 2) [IUI is a key biochemical event and is not an adverse health effect;](#) the committee recommended using a *nonadverse* effect rather than an *adverse* effect as the point of departure for the perchlorate risk assessment. Using a nonadverse effect that is upstream of the adverse effects is a [conservative, health-protective approach to the perchlorate risk assessment.](#)
- 3) [No adverse health effects will occur if IUI does not occur;](#)
- 4) [Changes in thyroid hormone levels are not necessarily adverse; the compensatory increase in TSH secretion and thyroid iodide uptake can return thyroxine \(T4\) and triiodothyroine \(T3\) production to normal without causing adverse effects on human](#)

health. The committee, however, does not view transient changes in serum thyroid hormone and TSH concentrations as adverse health effects; it considers them to be biochemical changes that could precede adverse effects.

5) The No Observed Effect Level (NOEL) value from Greer et al. (2002) is consistent with other clinical studies that have investigated IUI by perchlorate.

The NOEL of 0.007 mg/kg-day was established and used by the NRC as the point of departure for developing a reference dose (RfD). To derive the RfD, NRC divided the NOEL by an uncertainty factor (UF) of 10 to account for the most susceptible individuals in the population—hypothyroid or iodide deficient pregnant women and their developing fetuses. An RfD is generally derived from a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL). The NRC stated that “inhibition of iodide uptake by the thyroid is clearly not an adverse effect; however, if it does not occur, there is no progression to adverse health effects.”

Perchlorate is water soluble, is not metabolized by the body and is removed from the bloodstream by the kidneys. The half-life of perchlorate in the body is about eight hours. Because of this short duration, exposure to perchlorate must essentially be continuous for any level of perchlorate to remain in the body. Given the natural compensation mechanisms, NRC determined that it was likely that, in people with normal iodide uptake, reduction of iodide uptake by 75% for several months or longer would be required for thyroid hormone production to decrease enough to cause adverse effects. In adults, that would require sustained exposure to 0.4 mg/kg-day of perchlorate for a 70 kg person.

In reaching its conclusions, NRC relied on Greer et al. (2002) and on four other clinical studies in which healthy adults were administered perchlorate. NRC stated that in addition to these studies, studies of long-term treatment of hyperthyroidism, occupational studies, and studies of environmental exposure added confidence to the overall database. NRC relied exclusively on human studies, stating that, when available and reliable, human studies are preferred over animal studies.

The study subjects in Greer et al. (2002) were all free-living healthy adults, eating a self-selected diet. The baseline values of thyroid hormones varied somewhat among the subjects, but all were within the normal range. Although each individual study group was small, the results were consistent within each treatment group. The effects of similar doses of perchlorate on iodide uptake were also similar across all five studies. NRC stated that the reproducibility of the results across all five of the clinical studies, coupled with the results of studies of long-term treatment of hyperthyroidism and studies of environmental and occupational studies, strengthened its confidence in the NOEL value determined by Greer et al. (2002).

B. US EPA IRIS (2005). Perchlorate and Perchlorate Salts.

The US EPA IRIS assessment is based on NRC (2005). US EPA states

The NRC perchlorate committee took into consideration presentations at the

committee's public meetings, submitted public comments, and the comments made by technical experts on the draft NRC perchlorate report. The conclusions, recommendations and final content of the NRC (2005) report rest entirely with the committee and the National Research Council.

US EPA subsequently reviewed and accepted the NRC recommendations. It is this information that was used as the basis of the RfD presented in IRIS.

Furthermore,

The IRIS Summary has undergone review by EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Chronic Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents...

Lastly, US EPA did conduct an evaluation of the most sensitive population. They state:

Intraspecies Factor = 10. The intraspecies uncertainty factor accounts for variability in responses among humans, and is intended to protect populations that are more sensitive than the population tested. Because the critical study (Greer et al., 2002) for perchlorate was based on healthy adult men and women, an uncertainty factor of 10 is applied to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.

C. Agency for Toxic Substances and Disease Registry (ATSDR; 2008). Toxicological Profile for Perchlorates.

In its profile, ATSDR stated that: (1) exposure to perchlorate can occur by ingestion of food or water that contains perchlorate; (2) the main target organ for perchlorate toxicity is the thyroid gland; (3) perchlorate has been shown to partially inhibit the thyroid's uptake of iodide; (4) although not demonstrated in humans, it is anticipated that people exposed to excessive amounts of perchlorate for extended periods may experience decreased production of thyroid hormones; and (5) other chemicals, such as thiocyanate and nitrate, are also known to inhibit iodide uptake (p. 6-8).

ATSDR concurred with the NRC-recommended RfD of 0.0007 mg/kg-day for perchlorate. ATSDR stated that its decision was made after a careful evaluation of NRC (2005) and of studies published thereafter. ATSDR stated that Greer et al. (2002), upon which the RfD was based, was supported by other clinical studies, worker studies, and environmental studies.

ATSDR discussed the simultaneous joint effects of perchlorate and other competitive inhibitors of iodide uptake (p. 132). ATSDR stated that nitrate and thiocyanate are widely distributed in nature, and because both of these anions also inhibit iodide uptake, they must be included in any discussion of iodide inhibition. ATSDR noted that the effects of thiocyanate on thyroid function have long been known. ATSDR calculated that exposure to nitrate in drinking water at the current nitrate MCL level would cause inhibition of iodide uptake equivalent to 300 ppb of perchlorate in drinking water.

ATSDR also stated that the most sensitive populations to iodide uptake inhibition are fetuses and pre-term newborns (p. 134). ATSDR found no cases linking perchlorate to adverse health effects in fetuses or newborns in the scientific literature. The expected sensitivity of these populations is due to the important role played by thyroid hormones during development.

D. US EPA OIG (2010). *Office of Inspector General Scientific Analysis of Perchlorate.*

OIG stated that: (1) perchlorate acts by blocking iodide uptake into the thyroid; (2) dietary exposure to thiocyanate and nitrate also inhibits iodide uptake; and (3) iodine deficiency itself directly impacts iodide uptake. OIG concluded that it is the combined effect of iodine deficiency and exposure to thiocyanate, nitrate, and perchlorate that accounts for decreased iodide uptake in humans (p. 10).

OIG determined that a single-chemical risk assessment would not effectively address any public health issue associated with decreased iodide uptake (p. 11). As a result, OIG conducted a cumulative risk assessment, following the concepts in US EPA’s Framework for Cumulative Risk Assessment, to address the public health issues associated with low iodide uptake. OIG concluded that use of a cumulative risk assessment approach was necessary to accurately characterize the nature of the problem and to identify solution(s) (p. 28).

With regard to iodide deficiency, OIG stated that if the diet is poor in iodine, the amount of iodide uptake into the thyroid will be low regardless of exposure to thiocyanate, nitrate, and perchlorate (p. 48). Lack of iodine in the diet results in the same outcome as exposures to substances that inhibit the uptake of iodide. It is the combined effect of all four stressors on the thyroid (exposure to thiocyanate, nitrate and perchlorate, and lack of iodine in the diet) that determines the amount of iodide uptake (p. 39).

OIG stated that the public health issue (subtle mental deficits in children), is caused by an insufficient amount of iodide uptake in pregnant women, fetuses, and infants (p. 175). While any one of the four stressors (lack of iodide, or excess thiocyanate, nitrate or perchlorate) could potentially result in lowered iodide uptake, OIG concluded that focusing on only one of the four stressors would not address the public health issue in question.

THE SAB IS RAISING VALID SCIENTIFIC QUESTIONS AS A RESULT OF THIS NARROW SCOPE; HOWEVER, THE FULL DATABASE OF PERCHLORATE RESEARCH ADDRESSES THESE QUESTIONS

With this narrow scope, the SAB did not have the benefit of understanding what scientific studies and assessments have been made by authoritative bodies. I draw your attention to some examples:

- Questions were raised by SAB members regarding the breadth of scientific information. This is understandable given that the SAB was only directed to selected studies published after 2005. For example, an excellent concern was raised regarding animal studies that investigated the effect of maternal and early neonatal perchlorate exposure on neurodevelopment. Such studies have been conducted in rats ([York, 2004](#); [Bekkedal et](#)

[al., 2000](#)). These are well-conducted developmental psychopharmacological studies of behavior, learning, and memory in offspring of mothers treated with various doses of perchlorate in drinking water during gestation and lactation. These studies concluded that, even at doses up to 10 mg/kg-d of ammonium perchlorate, there were no neurodevelopmental changes in offspring.

- Questions were raised regarding what level of IUI is considered adverse. The US EPA White Paper states that this effect is “non-adverse” (p. 5). That the SAB was debating this issue underscores the need to provide the panel with the full database on perchlorate. As noted above, the question of whether IUI is an adverse effect and what level of IUI is adverse, has been addressed by many authoritative bodies.
 - 1) [US EPA IRIS](#): “Iodide uptake inhibition is a key biochemical event that precedes all potential thyroid-mediated effects of perchlorate exposure. Because iodide uptake inhibition is not an adverse effect but a biochemical change, this is a No Observed Effect Level (NOEL). The use of a NOEL differs from the traditional approach to deriving an RfD, which bases the critical effect on an adverse outcome. Using a nonadverse effect that is upstream of the adverse effect is a more conservative and health-protective approach to perchlorate hazard assessment.”
 - 2) [NRC](#): “To cause declines in thyroid hormone production that would have adverse health effects, iodide uptake would most likely have to be reduced by at least 75% for months or longer.”
 - 3) [US EPA OIG](#) (p. 6): “We determined that hypothyroxinemia [an effect downstream of IUI] occurs in pregnant women when the TIU [total iodide uptake] becomes less than or equal to 25% of normal.”
 - 4) [ATSDR](#) (p. 115): “In humans, relatively large doses of perchlorate (600–900 mg/day, 8–13 mg/kg/day) are required to deplete thyroidal iodine stores sufficiently to decrease serum levels of T4...”

These authoritative assessments were consistent in the assertion that IUI is a reversible, non-adverse effect, and that a point of departure based on the threshold for IUI is conservative and health protective. Recognizing this fundamental toxicological concept is critical: basing the point of departure for risk assessment on a NOEL for a non-adverse effect ensures no other effect will occur and allows any other study’s dose to be put into context.

MORE TIME IS NEEDED: THE SHORT TIME LINE FOR THE SAB’S WORK FURTHER LIMITS ITS ABILITY TO CONDUCT AN AUTHORITATIVE REVIEW

Secondly, I point to the extremely limited timeline the SAB was given in order to accomplish its task.

December 16	Public announcement of the intent to establish a SAB; nominations requested.
May 18	US EPA White Paper released publically
July 10	Public Comments on White Paper Due to US EPA

July 18/19	SAB meeting
August 9	SAB deadline for comments and statements from SAB to US EPA ¹
September 11- 18	US EPA to issue draft of SAB report publically ¹
September 19	Last day US EPA will accept information prior to telecom
September 25	US EPA to hold telecom and review US EPA draft report

Given that many of the SAB members were introduced to the breadth of the scientific database through public comments submitted on July 10th for the July 18th and 19th meeting, the SAB is expected to review the complete database of science for perchlorate from July 10th to August 9th—just less than one month. Constraining the SAB in this manner rushes what should be a thoughtful and exhaustive process. This is clearly inadequate time for review of scientific information.

I hope you and the SAB will consider these points and make attempts to complete your review with the proper scope and timeframe. I would be happy to answer any questions you might have.

Sincerely,
INTERTOx, INC.

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

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¹ As reported by Mr. Carpenter at the SAB Meeting on July 19th.