PSG
PERCHLORATE STUDY GROUP
A coalition of aerospace, defense, chemical and allied industries

P.O. Box 13222
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November 18, 2008

Dr. Deborah L. Swackhamer,
Chair
Science Advisory Board
Environmental Protection Agency

Dr. Joan Rose
Chair
SAB Drinking Water Committee
Environmental Protection Agency

Dear Dr. Swackhamer and Dr. Rose:

We read with great interest your November 5, 2008 letter to Administrator Johnson concerning EPA's preliminary determination on a national drinking water standard for perchlorate. This letter states that "the SAB strongly believes that there must be a compelling scientific basis to support a determination not to regulate perchlorate…" We completely agree. Through the efforts of EPA's Office of Water, Office of Solid Waste and Emergency Response, and Office of Research and Development over the last decade, the Agency has developed this compelling scientific basis.

First, the overall scientific literature concerning perchlorate's potential effects on human health is extensive. There are very few compounds subject to EPA regulation that can rest on multiple pillars of scientific evidence, including animal studies in multiple species, occupational studies, environmental epidemiology studies, and human clinical trials. There are also very few compounds in which the mechanism of action is clear and occurs with well-defined, non-adverse precursors. And, there are very few compounds that have been subject to a rigorous and comprehensive National Academy of Sciences (NAS) review of the health effects. As the NAS panel stated, unless these precursor effects occur, the subsequent adverse effects will not occur. To cite the NAS report,

> The committee emphasizes that inhibition of iodide uptake by the thyroid has been the only consistently documented effect of perchlorate exposure in humans. The continuum of possible effects of iodide-uptake inhibition caused by perchlorate exposure is only proposed and has not been demonstrated in humans exposed to perchlorate (with the exception that in patients with hyperthyroidism doses of 200 mg daily or higher may reduce thyroid secretion). More important, the outcomes at the end of the continuum are not inevitable consequences of perchlorate exposure.[1]

[1] National Academy of Sciences, *Health Implications of Perchlorate Ingestion*, 2005, at 165 (pdf version).

Although no longer the drug of choice in the clinic for treating thyrotoxicosis, perchorate is still used medically. For example, perchlorate is used to treat amiodarone (an antiarrhythmetic agent) induced thyrotoxicosis.[2] In other words, except for its deliberate medical use, exposure to perchlorate has not been shown to have caused reduced thyroid function in humans. In addition to the NAS conclusions, newer studies indicate that exposures to perchlorate at environmentally relevant levels have not been demonstrated to *cause* any effect on the health of persons.[3] The weight-of-evidence suggests that adverse effects do not occur following chronic exposures to perchlorate at doses much greater than the RfD.[4]

Second, this extensive scientific literature has undergone several major peer reviews. EPA convened peer review panels of its draft risk assessments in 1999 and 2002. The University of Nebraska Medical Center convened a State-of-the-Science Symposium and peer review in 2003. From October 2004 to January 2005, the NRC panel of 15 national experts held several meetings and solicited extensive public comment. While the SAB can contribute to the findings of these panels, EPA already has extensive, independent scientific analysis of perchlorate to underpin its final determination.

Third, in particular, the PBPK model referenced in the letter has already been extensively peer-reviewed. Furthermore, the EPA is conducting an independent external letter peer review of a draft report prepared by EPA's Office of Research and Development titled, Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-based Pharmacokinetic (PBPK) Modeling. This review is expected to be completed shortly. The underlying model and its expansions are already the subject of four peer-reviewed, published scientific articles.[5] Significantly, the NAS panel

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The noted dose of 200 mg/d is a conservative therapeutic value. When use of perchlorate to treat hyperthyroidism was common, doses of 400 mg/d were commonly prescribed, but were found to be slow to control thyrotoxicity and doses needed to be repeated 4 to 5 times/d, due to the rapid excretion of the drug. Although it still took an average of 9.4 weeks, doses of up to 2000 mg/d were given to reduce hyperthyroidism to a remission state (Wolff, 1998).

[2] J. Wolff, *Perchlorate and the Thyroid Gland*, Pharmacol Rev. 1998; 50(1):89–105.

[3] See, Benjamin C. Blount, *et al.*, *Perchlorate Exposure of the US Population, 2001-2002*, J Expos. Sci Envtl Epidem. 2006c; Benjamin C. Blount *et al.*, *Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United States*, Envtl Health Perspect., 2006b, 1865-71; Rafael Tellez Tellez *et al.*, *Chronic Environmental Exposure to Perchlorate Through Drinking Water and Thyroid Function During Pregnancy and the Neonatal Period*, Thyroid, 2005, 963-975; Yona Amitai *et al.*, *Gestational Exposure to High Perchlorate Concentrations in Drinking Water and Neonatal Thyroxine Levels*, Thyroid, 2007, 843-850; Craig Steinmaus *et al.*, *Impact of Smoking and Thiocyanate on Perchlorate and Thyroid Hormone Associationsin the 2001-2002 National Health and Nutrition Examination Survey*, Envtl Health Perspect, 2007, 1333-38.

[4] See, Tellez *et al.*, 2005; Amitai *et al.*, 2007; Lewis E. Braverman *et al.*, *The Effect of Perchlorate, Thiocyanate, and Nitrate on Thyroid Function in Workers Exposed to Perchlorate Long-Term*, J. Clin. Endocrinol. Metab., 2005, at 700.

[5] Rebecca A. Clewell *et al.*, *The Use of Physiologically-Based Models to Integrate Diverse Data Sets and Reduce Uncertainty in the Prediction of Perchlorate and Iodide Kinetics Across Life Stages and Species*, Toxicol. Ind. Health, 2001, 210-222; Rebecca A. Clewell *et al.*, *Predicting Fetal Perchlorate Dose and*

endorsed it as "the best available approach" for determining effects in sensitive subpopulations where experimentation is impossible. While we are not aware of the particular changes EPA staff made to the PBPK model for use in the preliminary determination, the *Federal Register* notice provides an estimate of predicted changes in iodine uptake inhibition (IUI) in sensitive subpopulations that do not differ significantly from the published findings in *Clewell et al. (2007)*. The results of this modeling estimate that certain sensitive populations (although not the most sensitive population, which are pregnant women and their fetuses) may have exposures in excess of the RfD. However, these groups would have minimal IUI at environmental doses. These conclusions are important enough to state again: even at doses greater than the reference dose, sensitive subgroups within the population may have minimal changes in their IUIs. The magnitudes of these changes are small enough to be attributable to normal fluctuations, possibly from diet. As noted by the NAS review, unless there is a sustained and significant change in IUI, adverse effects from perchlorate will not occur.[6]

Fourth, since the scientific literature on perchlorate is extensive, EPA can rely on multiple approaches to determine that there would not be a meaningful opportunity for risk reduction through a national drinking water standard. As the PSG has stated in its public comments to EPA's May 1, 2007 notice (see attached), EPA reached its conclusions through several approaches, all with ample scientific justification. The literature on human health effects from perchlorate consists mainly of clinical, occupational, or ecological studies. There are also some well designed animal studies that have contributed to the health effects database. As EPA has stated repeatedly, PBPK modeling allows the agency to give policy officials more scientific support for interspecies and intraspecies uncertainty factors. Following EPA's first draft risk assessment for perchlorate in 1998, Dr. Curtis Klaassen, the Chair of the external peer review panel stated, "…a predictive risk assessment for perchlorate is possible and should be pursued in the next iteration of this assessment."[7] EPA's consideration of its findings in its preliminary determination is exactly the use of compelling scientific information to support its policy decisions your November 5th letter endorses.

Fifth, EPA has extensive monitoring data from public water systems on perchlorate occurrence in drinking water. While your November 5th letter states perchlorate has "wide occurrence," EPA's UCMR 1 data suggests that drinking water perchlorate occurrence is much less frequent that other compounds (sodium, manganese, sulfate, and boron) for which EPA has determined Federal drinking water standards are not necessary. The monitoring data also show that, for an overwhelming majority of the US population served by public water systems, exposure to perchlorate in drinking water is at a concentration much less than

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Inhibition of Iodide Kinetics During Gestation: A Physiologically-Based Pharmacokinetic Analysis of Perchlorate and Iodide Kinetics, 2003, Toxicol. Sci., 2003, 235-55; Elaine A. Merrill *et al*., *PBPK Model for Radioactive Iodide and Perchlorate Kinetics and Perchlorate-Induced Inhibition of Iodide Uptake in Humans*, Toxicol. Sci., 2005, 25-43; Rebecca A. Clewell *et al.*, *Perchlorate and Radioiodide and Kinetics Across Life Stages in the Human: Using PBPK Models to Predict Dosimetry and Thyroid Inhibition and Sensitive Subpopulations Based on Developmental Stage*, J. Toxicol. Envtl Health, 2007, 408-28.

[6] See Note 1.

[7] Curtis Klaassen, US EPA Perchlorate Peer Review Workshop, 1999.

EPA's calculated HRL of 15 ppb. In fact, based on UCMR1, only 1.8% of public water systems had levels of perchlorate that were above the minimum reporting limit of 4 ppb.[8] Although unpublished, the EPA's merger of the NHANES-UCMR1 datasets study has been peer-reviewed.

While determining a "meaningful opportunity for risk reduction" is appropriately a policy decision it must be based on the best available scientific data. The best available data on perchlorate exposure suggest that very few individuals will be exposed to a dose of perchlorate greater than the RfD by drinking water with a perchlorate concentration above the HRL. Further, since the HRL is based on the NAS-recommended reference dose which is set at the no observed effect level (NOEL), which the NAS panel noted is a more conservative and health protective approach than using EPA's traditional approach of relying on the no observed adverse effect level (NOAEL)[9], along with an additional safety factor applied to it, the quantifiable incremental risk would appear to be very small.

Finally, if the SAB convenes any public meeting on perchlorate, the PSG would welcome an opportunity to present the scientific literature and our public comments. For over 10 years, the PSG has worked cooperatively with EPA, states, and other Federal agencies to provide the best available scientific information on perchlorate to assist public agencies. We look forward to any such opportunity with the SAB.

Sincerely,

Mr. Michael Girard
Chairman
Perchlorate Study Group

Cc: Marcus Peacock, Deputy Administrator
Benjamin Grumbles, Assistant Administrator, Office of Water
Cynthia Dougherty, Director Office of Ground Water and Drinking Water
Eric Burneson, Chief, Targeting and Analysis Branch
Suhair Shallal, SAB Designated Federal Officer

[8] US EPA, Unregulated Contaminant Monitoring Regulation 1 List 1 Assessment Monitoring, 1999.
[9] NAS at 169, (pdf version).