United States Environmental Protection Agency (U.S. EPA) Science Advisory Board (SAB)
Teleconference Meeting
March 29, 2013
Meeting Minutes

Date and Time: March 29, 2013, 1:00 a.m. to 4:00 p.m

Location: By teleconference only

Purpose: To conduct a quality review of an SAB draft review report providing advice on EPA approaches for deriving a Drinking Water Maximum Contaminant Level Goal for Perchlorate

Meeting Participants:

SAB Members

Dr. David T Allen, Chair
Dr. Joseph Arvai
Dr. Thomas Burbacher
Dr. Ingrid Burke
Dr. Thomas Burke
Dr. Edward Carney
Dr. Terry Daniel
Dr. George Daston
Dr. Costel Denson
Dr. Otto C. Doering, III
Dr. Joel Ducoste
Dr. David Dzombak
Dr. William Field
Dr. Cynthia M. Harris
Dr. Robert Johnston
Dr. Kimberly L .Jones
Dr. Bernd Kahn
Dr. Catherine Karr
Dr. Nancy K. Kim
Dr. Francine Laden
Dr. Cecil Lue-Hing
Dr. Elizabeth Matsui
Dr. Surabi Menon
Dr. James R. Mihelcic
Dr. Christine Moe
Dr. Eileen Murphy
Dr. James Opaluch
Dr. Martin Philbert
Dr. Stephen Roberts
Dr. William Schlesinger
Dr. Daniel Stram
Dr. Peter Thorne
Dr. Paige Tolbert
Dr. Jeanne VanBriesen
Dr. John Vena
Dr. R. Thomas Zoeller

Liaisons to the SAB:
Dr. Katherine von Stackleberg, Chair, Board of Scientific Counselors

SAB Staff:
Dr. Angela Nugent, SAB Staff Office, Designated Federal Officer (DFO)
Mr. Thomas Carpenter. SAB Staff Office, DFO for the SAB Perchlorate Advisory Panel

Other Attendees: Names of those who requested the teleconference call-in number are provided in Attachment A.

Meeting Summary:

Convene the meeting

Dr. Nugent formally opened the meeting and noted that this federal advisory committee teleconference of the SAB[1] had been announced in the Federal Register[2] (published March 6, 2013, 78 FR 14536-14537). The SAB is an independent, expert federal advisory committee chartered under the authority of the Federal Advisory Committee Act (FACA). The SAB is empowered by law, the Environmental Research, Development, and Demonstration Authorization Act (ERDDAA), to provide advice to the EPA Administrator on scientific and technical issues that support EPA's decisions. The DFO noted that the Federal Register notice announcing the meeting had provided the public with an opportunity to provide written and oral comment. There were two requests for oral comment. Five sets of written public comments[3] had been received on the draft SAB report to receive quality review. These materials had been provided to SAB members and posted on the SAB web page for the meeting (http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/3bb19c9b7e8c322385257aed006a01cc!OpenDocument&Date=2013-03-29). Attachment A lists members of the public who requested the call-in information for this advisory teleconference.

The DFO stated that the SAB consists entirely of special government employees (SGEs) appointed by EPA to their positions. As government employees, chartered SAB members are subject to all applicable ethics laws and implementing regulations. After reviewing information provided by members, the SAB Staff Office asked three chartered SAB members, Drs. George Alexeeff, Michael Dourson and Gina Solomon, to recuse themselves from Board deliberations on the topic of the teleconference to avoid potential appearance of a loss of impartiality.

Quality review of the draft report, *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate* [4]

Public Commenters

Dr. Allen introduced the first public commenter, Dr. Michael Dourson. Dr. Douson noted that his organization, Toxicological Excellence for Risk Assessment (TERA), had worked with the Perchlorate Study Group, had monitored perchlorate toxicology studies for the past nine years, and had published on the chemical. He noted that TERA would make studies available to SAB members upon request.

Dr. Dourson commended the panel for its composition and for its recommendation that EPA should begin to use a physiologically based pharmacokinetic (PBPK) model for the derivation of the Maximum Contaminant Level Goal (MCLG) for perchlorate.

He made three comments:

1. The panel focused on thyroid hormone changes as the critical effect and this is appropriate. PBPK modeling will need to be developed to extend analysis from current iodide uptake coverage to hormone changes.

2. There have been approximately ten additional epidemiology studies published on perchlorate since 2005 that can be examined to strengthen the rationale for the choice of critical effect. He suggested that the Tellez et al study, [Tellez, RT, Michaud P, Reyes C, Blount BC, Van Landingham, CB, Crump KS, et al. 2005. *Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period.* Thyroid 15(9):963–975], which is not an ecological study, included individual-specific levels of perchlorate in blood and urine for individuals in three different towns. These data would be useful for future modeling.
3. Several written public comments mention sufficient supplementing iodide in the diet as a risk management consideration. Supplementing iodide for women would be an important parameter for EPA to consider related to perchlorate.

The second public commenter was Dr. Richard Pleus of Intertox, who provided two sets of written comments on behalf of the Perchlorate Study Group. He also commended the composition and efforts of the panel. He voiced two concerns. First, the SAB panel only had limited time available for reviewing the toxicology and pharmacology of perchlorate, compared to the time taken by the National Research Council for developing its 2005 report. Second, the SAB draft report did not include specific recommendations related to dose-response assessment. Adding a dose-response discussion will help improve the report.

He also noted that the Greer et al. 2002 study (Greer M, Goodman G, Pleus R, Greer S. *Health effects assessment for environmental perchlorate contamination: The dose response assessment for inhibition of thyroidal radioiodine uptake in humans*. Environmental Health Perspectives, 2002; 110:927) is a reliable source of information on impacts of perchlorate on a pregnant women and her fetus. He called for the document to strengthen its discussion of impacts on the fetus and the question of the most sensitive population.

Presentation from the Panel Chair

Dr. David Allen introduced Dr. Stephen Roberts, Chair of the SAB Perchlorate Advisory Panel, and asked him to provide some background on the draft report as an introduction to the lead reviewers. Dr. Roberts expressed thanks for members' quality review comments[5] and for the public comments. He noted that page 6 of the draft report presents the standard approach to calculate an MCLG. This calculation involves a reference dose (RfD). The National Research Council (NRC) recommended the use of a precursor, non-adverse effect (i.e., inhibition of iodide uptake) to derive an RfD for perchlorate. EPA asked the SAB to provide advice on many topics: sensitive life stages, the MCLG derivation, PBPK modeling, recent epidemiological literature that might contribute to the MCLG, and how different sources of information can be integrated to develop a health-protective MCLG.

The SAB panel found that the traditional approach for generating the MCLG was not the best way to develop a perchlorate MCLG. The mode of action for perchlorate is well known. PBPK and pharmacodynamic (PD) modeling allows integration of many different kinds of scientific information into the MCLG. PBPK/PD modeling provides a "stepwise approach" for integrating data that can use available information and indicate additional research needs.

It was not the panel's intent to build the PBPK/PD model or to recommend a particular MCLG. Instead, the report recommended an approach to EPA and indicated the kinds of science to incorporate. The panel recommended a process for EPA to follow and emphasized the importance of transparency in developing its approach.

One of the consequences of recommending this novel approach was some difficulty in responding to charge questions framed for an alternative, more traditional MCLG approach. The panel tried to respond to the explicit questions asked while indicating new directions the EPA should take. As a result, the draft report suffers from redundancy. Dr. Roberts will consider ways to address those problems.

Dr. Roberts responded to the public commenters. He observed that Dr. Dourson agreed with the panel's recommendation that EPA should pursue a PBPK modeling approach. The panel report could note the studies identified by TERA and point EPA to those data so the agency can obtain them and integrate them.

Regarding Dr. Pleus's comments, he observed that the panel did not intend to develop a PBPK model or recommend a particular MCLG and therefore did not need additional time or expertise for those purposes. Dr. Roberts also noted that the panel defined sensitive life stages where thyroid-dependent brain development is occurring. These stages include fetuses, infants and early childhood. Dr. Roberts will consider adding references regarding impacts on fetuses. The draft report did not intend to identify infants as the most sensitive population. Instead, it recommends that EPA should consider all the life stages that involve thyroid-dependent brain development. As modeling and analysis develop, the implications for fetuses (and refinement of the MCLG) will become clearer.

Chartered SAB Discussion and Disposition of the Report

After Dr. Roberts completed his remarks, Dr. Allen asked the lead reviewers to briefly summarize their major comments in response to the SAB's four quality review questions:

- Were the charge questions adequately addressed?
- Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?
- Is the draft report clear and logical?
- Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Dr. Edward Carney, the first lead reviewer, commended the panel for an excellent report, which addresses current directions in science related to modeling and mode of action. He supported the pragmatic approach in the report, which he suggested should be more clearly explained. In the short term, the model addresses the critical effect using clinical observations. He suggested that available clinical research should be cited in the report. He suggested that the panel's response to EPA's question regarding estimating reductions in adverse health effects that are likely to result from reducing perchlorate levels in drinking water was too short. It would be appropriate to provide a sense of the magnitude of the problem, given available knowledge about mode of action. He recommended that the report acknowledge the merits of considering a cumulative

approach to risk management that would acknowledge the role of iodine and other goitrogens. He also mentioned a 2011 study published in the Journal of the American Thyroid Association (A. Stagnaro-Green et al., *Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartu*m, Thyroid 201, 11, pp. 1081-1125) that would be useful to cite.

Dr. Elaine Faustman, the second lead reviewer, expressed appreciation for the interesting and exciting report. She supported the staged approach, which balances the need for research vs. actions that can be taken quickly. She noted that her written comments identify several areas where the draft report could be clarified. These comments include: 1) clarifying whether the term "fetus" includes the stage of embryonic development in the first nine weeks; 2) more consistently emphasizing the availability of clinical and rodent reports, despite the limitations of the current epidemiology literature; 3) clarifying what should be done in the first stage recommended by the draft report; 4) recommending a process for evaluation that would allow EPA to consider the value of additional information; 5) consideration of other goitrogens; and 6) linking the discussion to EPA's Office of Research and Development's research related to Adverse Outcome Pathways. She also suggested that the report explain what hypothyroidism is more clearly, using language provided by SAB member Dr. Jeanne Van Briesen in her written comments.

Dr. Cynthia Harris, the third lead reviewer, also commended the advisory panel for its excellent work. She found that the draft report presented a thorough review of literature on the fetus and neonate, although it should be revised to discuss the literature on effects on infants and children more fully. She called for the report to provide a greater discussion of how EPA can use available data to develop the MCLG. More discussion of dose-response is needed. She agreed that PBPK/PD modeling provided a more comprehensive biological framework than the traditional RfD approach. She found it useful that the report contains a recommendation for communication strategies to explain the premise for how MCLGs are derived, using the whole body of evidence for developing a health-protective MCLG.

Dr. Martin Philbert, the fourth lead reviewer, agreed that the panel had developed a fine report. He viewed repetition of major points in the body of the report as necessary, but he suggested that the Executive Summary should be edited to remove repeated language. He agreed that some discussion of developing a dose-response estimate should be included.

Dr. Paige Tolbert, the fifth lead reviewer, concurred with other quality review comments. She congratulated the panel for its fine work, which integrates the latest science on mode of action, systems biology, epidemiology, and linkages between key events to advise EPA to develop a more modern risk assessment. Overall, Dr. Tolbert found that the epidemiologic section of the report was strong. She made a few points that she characterized as "subtle" to help with revising the draft SAB report. She noted that the report should identify ways that ecological epidemiology studies could contribute to understanding perchlorate impacts. Although those studies are not useful for the kinds of quantitative linkages that PDPB/PD models are trying to achieve, they can be used to help understand how people modify their exposure to the chemical. She also suggested that Appendix B on epidemiological data and PBPK/PD modeling be revised to more clearly discuss the benefits and tradeoffs of incorporating exposure data. Finally, she asked

whether the panel had considered recommending that EPA reanalyze existing data in light of emerging knowledge of the underlying biology related to perchlorate's effects.

Dr. Allen thanked the lead reviewers for their thorough comments and asked Dr. Roberts to respond to the reviewers' main points. Addressing Dr. Carney's point regarding references to available clinical data for developing the MCLG, Dr. Roberts noted that he would revise the draft report to provide examples of clinical data that could be used for MCLG development. The report would not provide an exhaustive literature review, however, because such a review would soon be out of date. Addressing Dr. Carney's point regarding estimating reductions in adverse health effects that are likely to result from reducing perchlorate levels in drinking water, Dr. Roberts acknowledged that the draft report's response was terse. A PBPK/PD model like the one being recommended for MCLG derivation could be used for estimating perchlorate concentrations in drinking water. The panel could make that point more clearly in the draft report.

In response to points made by several lead reviewers regarding development of a dose-response estimate, Dr. Roberts stated that the panel recognizes this question is important. Although the work of the panel was not designed to perform a dose-response analysis, the report could be revised to discuss the dose-response analysis and how that fits into the PBPK/PD modeling approach.

Dr. Roberts agreed to make clarifications related to Dr. Faustman's comments. He will revise the report to better explain the distinction between sensitive life stages vs. sensitive populations. The panel wished to address this issue with a special focus on exposures and viewed the fetus as a sensitive life stage, exposed through the pregnant woman. Additionally, he will: 1) clarify the use of the term "fetus;" 2) better link the epidemiology literature with the life-stage approach; 3) bolster citations related to infants and children; 4) discuss the utility of the model for other chemicals; and 5) consider whether the report should refer to Adverse Outcome Pathways. Dr. Roberts clarified that the report should not be interpreted to intend that EPA should delay action in developing an MCLG. The report should clearly communicate that EPA should take action on the basis of the available information.

Regarding Dr. Tolbert's comments, Dr. Roberts will clarify several technical points related to epidemiology. Given the priority assigned to other recommendations in the report, the panel did not judge it to be appropriate to recommend that epidemiology data be reanalyzed in light of new information emerging relating to the underlying biology.

After the panel chair had concluded his response to comments from the lead reviewers, other SAB members provided additional comments and questions.

One member noted that she had reviewed the draft report from the perspective of a clinician. She suggested that the report provide some better context for understanding terminology such as hypothyroidism and subclinical hypothyroidism and how these terms relate to one another. She suggested that it may be useful to describe the different clinical tests for hypothyroidism,
In regard to the comment that there was little information regarding infant and child exposure, she noted that there was a small published literature on hypothyroidism in children and that she

had provided these references in her written comments. Dr. Roberts acknowledged her comment and the value of defining the clinical terms. He will consider whether it will be important to catalogue clinical tests as she recommended.

Another member supported the high-level approach of the report but expressed some concern that the report only provides a schematic approach for deriving an MCLG. It does not describe how the MCLG would be derived. He asked whether the committee intended to lead to an "additional decade of delay" when there is a need for an MCLG. Dr. Roberts responded that it was not the intention of the panel to recommend that EPA must develop the whole model. There will need to be a step-wise process and identification of critical effect. The panel is not recommending using the traditional approach, but instead identifying a point of departure for the new PBPK/PD approach.

Another reviewer expressed appreciation for the quality of the draft report, which addressed a complicated issue. The mode of action for perchlorate, which leads to iodide uptake inhibition, is heterogeneous for different life stages. The literature on treatment for congenital hypothyroidism and thyroid hormone insufficiency could be helpful to assess the health effects of regulation. It may also be useful to consider variability. There is a small but important literature that could help generate a reference range. Such information would be useful to consider along with a dose-response assessment. Dr. Roberts responded that he would revise the report to add mention of treatment of thyroid insufficiency and the importance of a set point in the context of dose response.

Two final SAB members commented on the letter to the Administrator. They suggested that major recommendations be more clearly highlighted and that the executive summary provide a brief but informative description of the charge.

Dr. Allen and the DFO then informed members that Dr. Pleus had requested an opportunity to provide brief additional public comment. The Chair informed Dr. Pleus that he had two minutes for additional comment. Dr. Pleus noted that the draft report did not address the charge question regarding quantifying adverse effects and did not address how a dose-response estimate would be developed in the context of PBPK/PD modeling. Dr. Roberts responded that the report will be as specific as it can in suggesting a dose-response approach that EPA could implement. The report will better communicate the fundamental importance of dose-response estimation and how it fits into the model.

Dr. Allen asked if members had follow-up or clarifying questions for the public commenter. One member asked about the nature of studies that would be available to develop a dose-response. Dr. Pleus responded that there is information on impacts on thyroid hormone in the literature in humans and rodents.

After discussion had concluded, Dr. Allen asked for a motion to dispose of the report. He reminded members that the purpose of the quality review is to determine if the report is ready to transmit to the Administrator as an SAB report and under what conditions. Dr. Tom Burke moved that Dr. Roberts and his panel revise the report for the chartered SAB Chair to review before transmittal to the Administrator. Dr. Cynthia Harris seconded the motion. The motion was

approved unanimously. Dr. Allen concluded the discussion by thanking Dr. Roberts and his panel for their hard work.

The DFO adjourned the meeting at 2:45 p.m.

Respectfully Submitted	Certified as Accurate
___*/Signed/*_____	___*/Signed/*_____
Dr. Angela Nugent	Dr. David T. Allen
SAB DFO	SAB Chair

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

Attachment A: Members of the public attending the public meeting:

Nancy Beck, American Chemistry Council
Robert Benson, EPA
Scott Biernat, Association of Metropolitan Water Agencies (AMWA)
Miranda Brannon, US Air Force
Sarah Bresolin Silver, SBA Office of Advocacy
Eric Burneson,EPA
Natalie Cannon, EPA
Nancy Carrasco, Yale University
Gail Charnley, HealthRisk Strategies
Lisa Christ, EPA
Perry Cohn
Lisa Corey, Intertox
Todd J. Croft, Nevada Division of Environmental Protection
Joshua Das, Massachusetts Water Resources Authority (MWRA)
Catherine Davis, EPA
Casey Dietrich, CQ Transcriptions
Beth Doyle, EPA
William Eck, Health Effects Research Program
Michael Firestone, EPA
Malcolm Garg, U.S. Army
Mary Gilbert, EPA
Fredianne Gray, EPA
Maria Hegstad, Inside EPA
Ann Johnson, EPA
Dinesh Kumar, Chemical Watch
Annie Lumen, EPA
Gary R. Lynch, Park Water Company
Greg Malcolm, U.S. Army
David Mattie, Henry M. Jackson Foundation for the Advancement of Military Medicine
Anita Meyer, US Army Corps of Engineers
Darrell Osterhoudt, Association of State Drinking Water Administrators
Mary F. Ostrowski, American Chemistry Council
Santhimi Rathsanjami, EPA
Dave Reynolds, Inside EPA
Pat Rizzuto, BNA
Joanne Rovet, University of Toronto
Jim Rollins, Policy Navigation Group
Teri Sterner, Henry M. Jackson Foundation for the Advancement of Military Medicine

Materials Cited

The following meeting materials are available on the SAB website, http://www.epa.gov/sab, at the page for the March 29, 2013 teleconference: http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/3bb19c9b7e8c322385257aed006a01cc!OpenDocument&Date=2013-03-29

[1] Roster of SAB members and Liaisons

[2] Federal Register

[3] Written public comments:

- Comments from Gail Charnley, Health Risk Strategies, March 26, 2013.
- Public comment from Patricia Mulroy, Southern Nevada Water Authority. (
- Public comments from Richard Pleus, Intertox, dated March 18, 2013.
- Public comments from Richard Pleus, Intertox, March 22, 2013.
- Public comments from Tom Curtis, American Water Works Association.

[4] *SAB Advice (02/25/13 Draft) on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate*

[5] Preliminary Member Comments on the SAB Draft Report *SAB Advice (02/25/13 Draft) on Approaches to Derive a MCLG for Perchlorate*