

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD (SAB)
Quality Review Teleconference

June 6, 2011
12:00 – 2:30 p.m. Eastern Time

Minutes of the Meeting

Purpose: to conduct a quality review of a draft (May 4, 2011) SAB report, *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*.

Attendees:

Chartered SAB Members: Drs. Deborah Swackhamer (SAB Chair) (University of Minnesota), Timothy Buckley (Ohio State University), Terry Daniel (University of Arizona), George Daston (Procter & Gamble), Costel Denson (Costech Technologies), Otto Doering III (Purdue University), Bernd Kahn (Georgia Institute of Technology), Nancy Kim (Health Research Institute), Cecil Lue-Hing (Cecil Lue-Hing & Associates), L.D. McMullen (Synder & Associates), Eileen Murphy (Rutgers University), Duncan Patten (Montana State University), Stephen Roberts (University of Florida), Jerald Schnoor (University of Iowa), Kathleen Segerson (University of Connecticut), Paige Tolbert (Emory University), and John Vena (University of Georgia).

Designated Federal Officer: Stephanie Sanzone (EPA SAB Staff Office)

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

Meeting Materials:

All materials discussed at the meeting are available on the SAB website, <http://www.epa.gov/sab>, at the [June 6, 2011 SAB Meeting](#) page.

Summary of Discussions:

A. Opening Remarks

The meeting was announced in the Federal Register¹ and proceeded according to the meeting agenda², as revised. Stephanie Sanzone, Designated Federal Officer for the meeting, convened the meeting and noted that the chartered Science Advisory Board (SAB) operates in accordance with the Federal Advisory Committee Act. This means that meetings are announced and open to the public, meeting minutes are prepared, and all materials prepared for or by the SAB are available to the public. Ms. Sanzone noted that all SAB members participating in the meeting were in compliance with conflict of interest and ethics rules that apply to them. She noted that discussions on the call would reference a draft document prepared by the SAB Dioxin Review Panel, available on the SAB website³. A compendium of comments offered by SAB members⁴ on the draft report also is available on the website.

Ms. Sanzone noted that the SAB Staff Office had received a number of public comments⁵, which had been posted to the SAB website, and that eight individuals had registered in advance to provide oral

comments at the meeting (see List of Registered Speakers, attached to the meeting agenda²). She then turned the meeting over to the Chair of the chartered SAB, Dr. Deborah Swackhamer.

Dr. Swackhamer noted that the purpose of the meeting was to conduct a quality review of the draft SAB report (dated May 4, 2011) entitled, *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*. The chartered SAB must review and approve all SAB reports before they are transmitted to the Administrator. She indicated that there were no requests from the EPA for technical corrections or clarifications to the draft SAB report. She noted also that the agenda included up to an hour for public comment from registered speakers and an opportunity for SAB members to ask questions of the presenters if they so chose.

B. Overview of the Draft Report

Dr. Timothy Buckley, Chair of the SAB Dioxin Review Panel, gave an overview of the panel's process and conclusions. He referred to the rich history of the Agency's work on dioxin, including the 2003 EPA human health assessment for TCDD (dioxin) and the 2006 National Academy of Sciences (NAS) review of the EPA's analysis. He noted that the SAB had been asked to review EPA's response to the NAS recommendations regarding: dose-response modeling, including linear and nonlinear extrapolation methods; transparent selection of data sets; cancer weight-of-evidence assessment; physiologically based pharmacokinetic (PBPK) modeling; and the uncertainty analysis. Dr. Buckley summarized the EPA Charge to the SAB, which included a total of 45 questions in six categories. To address the charge, the SAB Dioxin Review Panel held two face-to-face meetings, and three public teleconferences to deliberate on the charge questions. Over 60 sets of written public comments and numerous oral presentations were received and considered during the review process.

Dr. Buckley summarized the panel's key findings, noting that the panel found the EPA report generally clear and responsive to many, but not all, of the NAS recommendations. The panel concluded that the process used to review the literature was comprehensive, rigorous and had included opportunities for public input. Dr. Buckley noted that the panel did find areas where the EPA document could be made more concise by moving some material to appendices. Deficiencies were noted in two areas: nonlinear dose-response and uncertainty analysis. Regarding the selection of data sets, the panel agreed that the report provided a clear definition of the process and that the criteria were well justified and applied, although the panel provided recommendations to further clarify the criteria for inclusion and exclusion of studies. The panel also noted that the report could be enhanced by including studies of dioxin-like compounds in the cancer weight-of-evidence. The panel agreed that the Emond PBPK for internal dose estimation provides the best available basis for the analysis, and supported the use of blood level as a dose metric. The panel also supported the use of two co-critical epidemiological studies for derivation of the reference dose. For the cancer assessment, the panel agreed that dioxin is carcinogenic to humans, but one panel member offered a dissenting view. The panel further recommended that the weight-of-evidence characterization draw upon all available types of data, and that the mode of action be characterized as "reasonably well known." The panel agreed with the use of the Cheng et al. study based on the NIOSH occupational cohort, and agreed that it is appropriate to use all-cancer mortality as the basis for the oral slope factor. The panel concluded that the EPA report did not respond to the NAS recommendation to adopt both linear and nonlinear alternatives for the cancer endpoint. The panel disagreed with EPA's conclusion that an uncertainty analysis is not feasible and the panel suggested several methods that could be used for such an analysis.

C. Public Comments

Mr. David Fischer, American Chemistry Council, commended the panel for its work and for providing important guidance on deficiencies in the EPA assessment. He requested that the SAB augment its report to ask the Agency to conduct a full weight-of-evidence analysis, rather than relying just on the Cheng et al. study. He noted that other studies do not show effects. In addition, he requested that the SAB report be strengthened to: ensure that the EPA report includes nonlinear approaches to the cancer reference dose; comment on the Toxic Equivalency Factors (TEFs) approach; recommend a no-observed-adverse-effect-level (NOAEL) based on human epidemiological data; and reference EPA guidance on quantitative uncertainty analysis. Mr. Fischer noted that subsequent speakers would elaborate on these issues.

Dr. Hans-Olov Adami, Harvard School of Public Health, offered comments on behalf of the American Chemistry Council. He made three points in his remarks. First, he urged the Agency to consider the full body of evidence, and not bias the results by excluding negative studies. Second, he noted that the SAB report does not comment on EPA's poor adherence to the 2005 cancer guidelines with respect to inclusion of negative studies. Third, he noted that EPA's use of all cancers for the dose-response modeling may generate an apparently consistent increase in all cancers, but consistent specific cancer results would still be needed.

Dr. Lesa Aylward, Summit Toxicology, indicated that she had reviewed the reference dose derivation on behalf of the Chlorine Chemistry Council. She concluded that a weight-of-evidence evaluation, including results from numerous human studies on infant thyroid status, shows no statistically significant TCDD effect, thus supporting a NOAEL. Dr. Aylward also identified several sentences in the draft SAB report that she felt were inaccurate, including an incorrect statement that Baccarelli et al. had used zonal averages in blood TCDD levels when calculating reference dose.

Dr. Lorenz Rhomberg, Gradient Corp., noted that he had received support from the American Chemistry Council, but that the comments were his own. He noted that the SAB panel has raised important concerns about the weight of evidence and the transparency of EPA's approach. He noted further that the SAB panel's conclusions about what is required are consistent with other panel reports from the SAB, but that EPA is still not addressing these issues. He urged the SAB to make a strong statement in the final SAB report to foster application of a sound risk assessment methodology at EPA, including quantifying uncertainty in risk analyses. In closing, Dr. Rhomberg questioned the use of the "all cancers" approach when there is no plausible mode of action for all cancers.

Dr. Robert Budinsky, Dow Chemical Co., commended the SAB for noting that EPA has not responded to the NAS recommendation to apply the 2005 cancer guidelines. He emphasized that in his view the Agency has a contradictory stance on mode of action (MOA), first indicating that an MOA exists and supports the use of a linear model of all cancers, but also concluding that no MOA can be determined from animal studies. He urged the SAB to recommend that EPA evaluate the MOA literature and criticize, rather than commend, EPA on this topic.

Dr. Laurie Haws, ToxStrategies, Inc., offered comments on behalf of U.S. Magnesium. She agreed with many of the panel's recommendations, but noted that the panel had failed to address other short-comings or to apply appropriate recommendations and had inappropriately ventured into policy issues. Dr. Haws recommended that the chartered SAB send the report back to the panel for additional work, including a stronger statement that EPA should address the strengths and weaknesses of the Baccarelli et al. study.

She also urged the SAB to consider revising the report to more strongly recommend that uncertainty analysis be presented.

Dr. Daniele Wikoff, ToxStrategies, Inc., provided comments on behalf of TR Solutions. She noted that the panel has provided inconsistent recommendations to EPA regarding the adequacy of evidence to support an MOA and a nonlinear cancer model, and requested that this point be clarified in the SAB report. She also requested that the SAB more clearly ask the Agency to use a weight of evidence consistent with the EPA guidance, including studies that show no effect. She noted that the panel should support its statement regarding convincing evidence of effects, stating her view that the panel (with the exception of Dr. Rozman's minority viewpoint) had overlooked the lack of statistically significance evidence of an increase in any type of cancer and had not supported this statement in the report.

Ms. Patricia Casano, General Electric Co., stated that there is no justification for the panel's suggestion that non-TCDD studies be used to bolster EPA's assessment. She noted her view that TEFs developed by the World Health Organization (WHO) cannot be assumed to be valid for human health risk assessment since research finds that results from laboratory rodents do not hold for humans. She stated that the SAB report should not suggest that reliable conclusions can be drawn using TEFs for non-TCDD compounds, and noted that GE requests that the draft report be returned to the panel to remove those references from the report.

Following the public comments, Dr. Swackhammer offered SAB members an opportunity to ask questions or provide comments in response to the public comments. Dr. Buckley noted that the points raised by the public speakers also had been made to the panel, and he assured the SAB that these comments had been considered by the panel.

D. SAB Member Discussion

Dr. Swackhamer opened the chartered SAB discussion of the draft report, reminding members of the quality review questions:

1. Were the original charge questions to the SAB Panel adequately addressed?
2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Panel's report?
3. Is the Panel's report clear and logical?
4. Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?

She requested the SAB lead reviewers—Drs. George Daston, Steve Roberts, Paige Tolbert and John Vena—to lead off the discussion by providing their answers to the quality review questions.

Dr. Daston commended the panel for its efforts. He stated that the charge questions had been addressed and that he had noted no technical errors or omissions. He suggested several areas where the SAB report could be clarified. He noted that the panel's language about MOA was inconsistent and he requested a more explicit statement that dioxin is a very well-studied compound and so it should be possible to use MOA as the basis for extrapolation. He noted that the draft SAB report does discuss uncertainty analysis, and includes (on p. 47) a good set of questions that might be the basis of an uncertainty analysis. He asked whether the SAB should recommend that EPA focus on these elements. He also recommended strengthening the recommendations on use of dioxin-like compounds, noting that weight

of evidence including these compounds can be helpful in MOA, plausible individual effects, etc. Dr. Daston suggested that the Hill coefficient could be set to “1” and the discussion on this topic could be shortened in the SAB report. He stated that the SAB report was very clear and logical. Regarding the panel’s recommendation that EPA have a technical editor revise the dioxin report, he suggested that it might also be necessary to develop a longer summary to supplement the short executive summary and the full report. In closing, Dr. Daston concluded that the panel’s conclusions were supported, with two exceptions: the recommendation that EPA delete the language about “outside the range of variability” when discussing animal studies, and the choice of study on decrease in sperm count. He requested that these two points be clarified in the report.

Dr. Roberts commended the panel for its hard work. He noted that the charge questions had been adequately addressed, the report was generally clear and logical, and he found no technical errors or omissions. He did request several clarifications, as noted in his written comments. Regarding the sperm count and motility as a NOAEL from Baccarelli et al., he noted that the panel had focused on whether this is an effect, rather than on the question of using that study to develop the NOAEL. He added that he agreed with a commenter that he was not sure the decrease in sperm count was a biologically meaningful reduction. He also noted that the charge question about the EPA approach for selecting studies was not clearly answered. In general, Dr. Roberts noted that SAB reports tend to say what the Agency has done well and what improvements are needed. Based on the public comments, this approach may be creating confusion about the SAB’s conclusions and recommendations. For the present report, the SAB letter needs to provide a clear response on the use of linear and nonlinear models for dose-response extrapolation and on the issue of uncertainty analysis. He also recommended that the format for providing recommendations (e.g., as bullets) be consistent throughout the report.

Dr. Tolbert provided her assessment that the panel had conducted a very thorough and balanced review of a lengthy EPA document. She noted that the panel’s conclusions were compelling and that the report included thorough and thoughtful responses to the EPA charge questions. Given the large number of recommendations, Dr. Tolbert suggested that the SAB report more explicitly prioritize the recommendations to suggest which recommendations should be done before EPA finalizes the dioxin assessment versus others that could be pursued later (e.g., as on-line addenda or in future updates as the science continues to evolve). She noted also some inconsistency in the presentation style for the recommendations and recommended that the report use a format that includes a response section with supporting discussion and rationale, followed by a succinct recommendation. In light of the dissenting opinion, Dr. Tolbert noted that the report should include some additional discussion of how the majority view diverged from the dissenting opinion. She highlighted some editorial comments, including the need for a clear discussion of the rationale behind the decision to use all-cancer mortality (given the multiple target organs). In closing, Dr. Tolbert said she was confident that the panel had the appropriate expertise needed to consider the public comments.

Dr. Vena echoed the other lead reviewers in complimenting the panel for its work. He noted that the report included well-articulated responses to the charge questions and the two appendices were excellent. He did not see any technical errors and thought the letter effectively highlighted the recommendations. He did note that the executive summary needed some revision and should have section headings for clarity. He recommended that the sections in the executive summary match those in the body of the report. He also recommended that some of the recommendations (e.g., responses to Charge 1.2, 2.2 and 2.3) be further clarified, as noted in his written comments. In sum, Dr. Vena commented that the report was well-written and referenced, and the conclusions and recommendations were well-justified.

Dr. Swackhamer thanked the lead reviewers, noting that many of their comments were consistent and that some of the comments echoed those of the public commenters. She then asked Dr. Buckley to respond to the lead reviewers.

Dr. Buckley thanked the reviewers for their comments. He acknowledged that the report had been developed by a large panel, with many members contributing in their own styles, and the draft report reflects these differences. He agreed that the inconsistencies identified by SAB members could be addressed. However, he cautioned that some of the language that SAB reviewers have commented on reflects careful wording that the panel was able to agree to. He noted that few chemicals are as challenging as dioxin from a risk assessment perspective and people can disagree on the interpretation of the data, as evidenced within the panel and between panelists and public commenters.

In response to Dr. Daston's comments about whether the MOA for dioxin was "reasonably well known," Dr. Buckley noted that the panel was comfortable with that language. Regarding dioxin-like compounds, he noted that there had been discussion within the panel about whether or not to consider information on dioxin-like compounds. The panel had concluded that EPA should consider these compounds in the assessment, but in a qualitative rather than a quantitative sense. Dr. Buckley agreed that the suggestion for a "long-form executive summary" was a good one, noting that the panel had discussed this also and the report could include this recommendation. He noted further that the report could be revised to accommodate the comments about "outside the normal range of variability." He indicated that the recommendation on the public health impact of a 20 percent reduction in sperm count could be strengthened. He noted that the panel had supported EPA's use of the Mocarelli et al. study. The strengths and weaknesses of the study should be discussed in EPA's report. It is important to consider null studies.

In response to Dr. Roberts' comments regarding the reduction in sperm count, Dr. Buckley agreed that the report language had side-stepped the actual mention of the LOAEL and he agreed to tighten up that discussion to say that the study is appropriate for development of a LOAEL. He acknowledged that the discussion of the linear versus non-linear extrapolation was sparse relative to the discussion of uncertainty analysis and that additional language would further explain why other extrapolation approaches should be considered. He further agreed to make sure a consistent style was used to present the recommendations.

In response to Dr. Tolbert's request that the priority of recommendations (near term versus longer term) be clarified, Dr. Buckley noted that the panel had not discussed the issues in that context. Instead, the panel had indicated highest priority recommendations by using "strongly recommend" or similar language. He noted that the report reflected the challenge of reaching consensus within the panel, but agreed to consider whether the letter needed to be revised to better reflect the relative priority of the recommendations. Regarding the dissenting opinion, Dr. Buckley responded that the panel is clear in its conclusion that TCDD is a human carcinogen, but the dissenting opinion is highlighted in the letter and also could be mentioned in the executive summary. Dr. Eileen Murphy noted that there is precedent for acknowledging and attaching a dissenting opinion to an SAB report, and stated that she would have liked more information on the dissenting opinion.

Regarding comments from Dr. Vena, Dr. Buckley agreed to clarify how the charge questions are labeled in the executive summary, and to clarify the recommendation for how to deal with null studies. With

respect to qualitative discussion of dioxin-like compounds, he agreed to clarify how this information might inform a weight-of-evidence assessment.

Dr. Swackhamer noted that editorial suggestions provided in member comments would be addressed and did not need to be discussed on the call. She then opened the floor for comments by other SAB members.

Regarding the minority opinion, Dr. Denson emphasized that the report should provide more detail on the nature of the dissenting opinion. Dr. Segerson suggested that the panelist be asked to expand on the technical rationale for his dissent. Dr. Buckley noted that the panel consensus had been in support of using the Cheng et al. (2006) study for cancer slope factor and dose-response, with Dr. Rozman dissenting from that conclusion. He suggested that part of the difference of opinion may arise from the different disciplines of the panelists. He noted that Dr. Rozman was an excellent toxicologist, but that much of the evidence being used was epidemiology; these two scientific disciplines use different approaches to understand risks (i.e., through the animal response literature versus human epidemiological studies). Dr. Daniel noted that this context would be useful to readers of the report.

The following additional points were raised by members:

- Dr. Swackhamer suggested that the phrase “state of the world” be replaced with a more scientific phrase.
- Dr. Daston noted that the appropriateness of sperm decrease as a LOAEL depends on the strengths and weakness of the Baccarelli et al. study.
- Dr. Kim noted that the report could provide more detail to support the panel’s conclusion that the Baccarelli et al. study was an appropriate basis for the reference dose.
- Dr. Patten noted that the report is somewhat inconsistent, in that it concludes that the EPA report is well-written but then recommends a number of revisions.
- Drs. Schnoor and Daston asked for clarification regarding the Hill coefficients, including the units and the use of a coefficient value of one.

E. Report Disposition

Dr. Swackhamer reminded SAB members of the options available for disposition of the Dioxin Review Panel’s report:

- Option 1: Approve the report, with the discussed changes, subject to final review by the SAB Chair;
- Option 2: Approve the report with edits, subject to final review by designated Board members and the SAB Chair; or
- Option 3: Return the draft report to the Dioxin Review Panel for further work, followed by a second Quality Review by the Board.

She then indicated her readiness to entertain a motion. Dr. Murphy made a motion to approve the draft report with review by several SAB members (Option 2). Dr. Daston seconded the motion. Dr. Swackhamer opened the floor for discussion of the motion. There being none, she called for a voice vote on the motion. Dr. Buckley abstained because of his participation on the authoring panel. All members participating in the voice vote signified approval of the motion.

Dr. Swackhamer then asked if the lead reviewers were willing to give a final review to the revised report, and Drs. Daston, Roberts, Tolbert and Vena agreed to provide that review. Dr. Swackhamer thanked Dr. Buckley for a great job tackling a large amount of information, and turned the meeting over to the Designated Federal Officer.

F. Adjournment

There being no further business, Ms. Sanzone adjourned the meeting at 2:30 p.m.

Respectfully Submitted,

/s/

Stephanie Sanzone,
Designated Federal Officer
SAB Staff Office

Certified as Accurate,

/s/

Dr. Deborah L. Swackhamer,
Chair
Science Advisory Board

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by SAB members during the course of deliberations at the meeting. Such ideas, suggestions and deliberations do not necessarily reflect consensus advice from the SAB. The reader is cautioned not to 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. Persons requesting the call-in number for the June 6, 2011, chartered SAB teleconference. (The actual attendance of all individuals on the call was not verified.)

Hans-Olov Adami, Ph.D.
Harvard School of Public Health

Lesa Aylward, Ph.D.
Summit Toxicology

Craig S. Barrow, Ph.D., DABT
Craig Barrow Consulting

Nancy Beck
U.S. Office of Management and Budget

Norman Birchfield, Ph.D.
National Center for Environmental Assessment
U.S. Environmental Protection Agency

Robert Budinsky, Ph.D.
Dow Chemical

Patricia Kablach Casano
General Electric Company

Becki Clark
National Center for Environmental Assessment
U.S. Environmental Protection Agency

Kathleen Deener
U.S. Environmental Protection Agency

Hisham El-Masri
U.S. Environmental Protection Agency

John L. Festa, Ph. D.

David Fischer
American Chemistry Council

Annette Gatchett
U.S. Environmental Protection Agency

Jonathan Gledhill
Policy Navigation Group

Barbara Gutierrez

U.S. Environmental Protection Agency

Laurie Haws, Ph.D.
ToxStrategies, Inc.

Maria Hegstad
Risk Policy Report
Inside Washington Publishers

Van P. Hilderbrand Jr.
Sullivan & Worcester LLP

Cheryl Hogue
Chemical & Engineering News

Jeremy P. Jacobs
Environment & Energy Publishing, LLC

Katharine Kurtz
Navy and Marine Corps Public Health Center

Deborah R. MacKenzie-Taylor, Ph.D.
Michigan Department of Environmental Quality

Clarence W. Murray, III, Ph.D.
Center for Food Safety and Applied Nutrition

Olga V. Naidenko, Ph.D.
Environmental Working Group

Tracie Phillips, Ph.D.
Texas Commission on Environmental Quality

Resha M. Putzrath, Ph.D., DABT
Navy and Marine Corps Public Health Center
Portsmouth, VA

Glenn Rice
U.S. Environmental Protection Agency

Lorenz Rhomberg, Ph.D.
Gradient Corp.

Pat Rizzuto
BNA, Inc.
Daily Environment Report

Jim Rollins
Policy Navigation Group

John D. Schell, Ph.D.
Center for Toxicology and Mechanistic Biology
Exponent

Charles Schlittler

Allen Silverstone, Ph.D.
SUNY Upstate Medical University

Thomas B. Starr, Ph.D.
TBS Associates

Jeff Swartout
U.S. Environmental Protection Agency

Linda Teuschler
U.S. Environmental Protection Agency

Daniele Wikoff, Ph.D.
ToxStrategies, Inc

Linda M. Wilson
NYS Office of the Attorney General

Materials Cited

The following meeting materials are available on the SAB website, <http://www.epa.gov/sab>, at the [June 6, 2011, SAB Meeting page](#).

¹ Federal Register Notice Announcing the Meeting (76 FR 26290-26291)

² Meeting Agenda, chartered Science Advisory Board, June 6, 2011

³ Draft (05-04-11) *SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*

⁴ Pre-Meeting Comments from SAB Members on the draft report, *Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*

⁵ Public Comments Received:

- Comments from Bob Budinsky, Dow Chemical Co.
- Comments from ENVIRON, on behalf of the American Chemistry Council
- Comments from Lesa Aylward, Summit Toxicology
- Comments from Lorenz Rhomberg, Gradient Corp.
- Comments from Patricia Casano, General Electric Co.
- Comments from Paul Noe, American Forest & Paper Assoc., and Robert Glowinski, American Wood Council
- Comments from the American Chemistry Council, Chlorine Chemistry Division.
- Comments from Judith Nordgren on behalf of the American Chemistry Council (June 20, 2011)