Summary Minutes of the
US Environmental Protection Agency
EPA Science Advisory Board
Dioxin Review Panel
Public Meeting
July13-15, 2010

ATTENDANCE

SAB Panel Members
Dr. Timothy Buckley (Chair)
Dr. Harvey Clewell
Dr. Louis Anthony (Tony) Cox
Dr. Elaine Faustman
Dr. Scott Ferson
Dr. Jeffrey Fisher
Dr. Helen Håkansson
Dr. Russ Hauser
Dr. Paige B. Lawrence
Dr. Michael I. Luster
Dr. Paolo Mocarelli
Dr. Victoria Persky
Dr. Sandra L. Petersen
Dr. Karl Rozman
Dr. Arnold Schecter
Dr. Allen E. Silverstone
Dr. Mitchell J. Small
Dr. Anne Sweeney
Dr. Mary K. Walker

SAB Staff Office
Dr. Thomas Armitage, Designated Federal Officer (DFO)
Dr. Vanessa Vu, Director

EPA's National Center for Environmental Assessment
Dr. Peter Preuss, Director
Dr. Belinda Hawkins
Dr. Glenn Rice
Dr. Jeff Swartout

Other Attendees (with their affiliations as entered on the sign-in sheets)
Dr. Diana Wong, SAB Staff Office, Designated Federal Officer
Dr. Hisham El-Masri, ORD
Linda Tuxen, ORD
Dr. Linda Teuschler, ORD
Dr. Abdel Kadry, ORD

Annette Gatchett, ORD
Janet Hess-Wilson; ORD
Mike Wright;, ORD
Norman Birchfield, ORD
Kathleen Newhouse, ORD
Morisa Spassova; ORD
Paul White, ORD
Ghazi Dannan, ORD
Rebecca Clark; ORD
Bob Budinsky, Dow Chemical
Thomas Starr, TBS Associates
Lesa Aylward, Summit Toxicology
Roger Cooke, RFF
Laura Anderko, Georgetown University
Jay Silkworth, GE
David Fisher, ACC
Dale Hattis, Clark University
William Mendez, ICF
Yvette Lowney, Exponent
Karen Hentz, Exponent
Resha Putzrath, Navy
Cara Henning, ICF
Andy Shapiro, ICF
Paul Villeneuve, Risk Sciences
Pat Casano, GE
Claude Emond, U. of Montreal
Scott Bartell, University of California
James Van Der Senalie, ACC
Cheryl Hogue, C & E News
Catherine Cooney, Chemical Watch
Maria Hegstad, Inside EPA
Jack Vanden Heuvel, Penn State University
Katie Burns, IFIC
Marcus Cooke, CCT
Mark Lee, ICF
Sandrine Deglin, Exponent
James Lamb, Exponent
Nancy Beck, OMB
Craig Barren, Consultant
Michele Roberts, AEHR
Mike Schade, CHEJ
Olga Naidenko, EWG
Rick Reiss, Exponent
Laurie Holmes
Margaret MacDonell, Argonne National Laboratory
Madelline Stano, AEHR

John DeSesso, Exponent
Todd Abel, ACC
Maggie Person, CHEJ
Chris Curry, CHEJ
Ted Verheggen, Dow
Lynn Thorp, CWA
Azita Mashayekhi, Teamsters
Tim Cheek, PNL

MEETING MATERIALS

The following meeting materials were available prior to or during the July 13-15, 2010 meeting, and were available on the general SAB web site at, **http://www.epa.gov/sab** and specifically at the following URL: **http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/3a85088bde1b4f32852576da0077a8c4!OpenDocument&Date=2010-07-13**

- FEDERAL REGISTER NOTICE
- MEETING AGENDA
- PANEL ROSTER
- AGENCY REVIEW DOCUMENTS
  Dioxin Reassessment - Response to the National Academies of Science
  PDF for EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (Main Text, part 1 of 2) (PDF, 691 pp., 7,739,250 bytes)

  Dioxin Reassessment - Response to the National Academies of Science
  PDF for EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (Appendices, Part 2 of 2) (PDF, 1,159 pp., 6,584,921 bytes)

- CHARGE TO THE COMMITTEE
  ORD Memo Dated May 27, 2010 (PDF, 7 pp., 341,452 bytes)

- PUBLIC COMMENTS
  Comments from David B. Fischer on behalf of the Chlorine Chemistry Division of the American Chemistry Council (PDF, 122 pp., 5,061,469 bytes)

  Comments from Donald L. Hassig, Cancer Action NY (July 7, 2010). (PDF, 2 pp., 21,475 bytes)

  Comments from Donald L. Hassig, Cancer Action NY (July 3, 2010). (PDF, 3 pp., 12,390 bytes)

  Comments from F. Edmond Johnston, III, E.I. du Pont Nemours and Company (DuPont) (PDF, 2 pp., 101,902 bytes)

Comments from Gary M. Williams, New York Medical College . (PDF, 2 pp., 44,625 bytes)

Comments from Gregory G. Bond, Dow Chemical Company (PDF, 7 pp., 68,967 bytes)

Comments from G. Thomas Tripp, U.S. Magnesium LLC (PDF, 2 pp., 98,128 bytes)

Comments from Jane Houlihan and Olga V. Naidenko, Environmental Working Group (PDF, 14 pp., 273,659 bytes)

Comments from Janet Gray on behalf of the Breast Cancer Fund (PDF, 3 pp., 128,572 bytes)

Comments from Jay Silkworth (July 9, 2010). (PDF, 4 pp., 127,729 bytes)

Comments from Jonathan Urban, ToxStrategies (PDF, 8 pp., 1,441,883 bytes)

Comments from Joshua T. Cohen, Tufts Medical Center (PDF, 2 pp., 36,053 bytes)

Comments from Laura Ford Brust, Sullivan and Worcester LLP, on behalf of Emhart Industries, Inc. (PDF, 15 pp., 301,311 bytes)

Comments from Mike Schade, Center for Health Environment and Justice. (PDF, 60 pp., 6,600,516 bytes)

Comments from Patricia Kablach Casano, General Electric Company (PDF, 78 pp., 626,156 bytes)

Comments from Traylor Champion, Georgia Pacific (PDF, 21 pp., 289,880 bytes)

Comments from William J. Waddell and John Doull, University of Kansas Medical School (PDF, 3 pp., 72,345 bytes)

Comments of Thomas B. Starr on behalf of the American Forest and Paper Association (PDF, 16 pp., 310,350 bytes)

EPA Docket Comments, July 9, 2010. (PDF, 5 pp., 51,534 bytes)

List of Public Speakers (PDF, 3 pp., 28,614 bytes)

Oral statement from Azita Mashayekhi, International Brotherhood of Teamsters (PDF, 2 pp., 98,995 bytes)

Oral statement from Carol Johnston, Ironbound Community Corporation (PDF, 2 pp., 19,754 bytes)

Oral statement from Delma Bennett, Mossville Environmental Action Now (PDF, 2 pp., 553,823 bytes)

Oral Statement from Lynn Thorp, Clean Water Action (PDF, 1 pp., 51,252 bytes)

Oral statement from Michele Roberts, Advocates for Environmental and Human Rights (PDF, 2 pp., 507,578 bytes)

Presentation from Jay B. Silkworth (PDF, 7 pp., 117,860 bytes)

Presentation from John M. DeSesso (PDF, 15 pp., 482,247 bytes)

Presentation from Lesa L. Aylward (PDF, 11 pp., 1,869,542 bytes)

Presentation from Robert Budinsky (PDF, 4 pp., 118,435 bytes)

Presentation from Thomas B. Starr, TBS Associates, on behalf of the American Forest and Paper Association and American Wood Council. (PDF, 8 pp., 1,015,050 bytes)

PURPOSE

The SAB Dioxin Review Panel held the first face-to-face meeting to begin its review of *EPA's Reanalysis of Key issues Related to Dioxin Toxicity and response to NAS Comments (May 2010 External Draft)* and discuss its preliminary responses to EPA's charge questions.

LOCATION

Hilton Washington Embassy Row, 2015 Massachusetts Ave. NW,
Washington, D.C. 20036

DATE AND TIME

The meeting was held on July 13, 2010 from 9:00 a.m. to 5:15 p.m. (Eastern Time), July 14, 2010 from 8:30 a.m. to 5:00 p.m. (Eastern Time), and July 15, 2010 from 8:30 a.m. to 2:30 p.m. (Eastern Time).

MEETING SUMMARY

The discussion generally followed the meeting agenda unless it was noted in the meeting summary below.

Tuesday, July 13, 2010

Convene the Meeting and Welcoming Remarks

Dr. Thomas Armitage, Designated Federal Officer (DFO) opened the meeting at 9:00 a.m. He stated that the EPA Science Advisory Board (SAB) operates under the rules and regulations of the Federal Advisory Committee Act (FACA) which required that all meetings where discussions and deliberations take place must be held in public. He informed that the SAB Panel members are in compliance with federal ethics requirements. He stated that one Panel member, Dr. Paolo Mocarelli, had indicated that he would recuse himself from any discussion pertaining to the use of his own study for the derivation of the reference dose for dioxin. Dr. Armitage stated that as DFO, he would be present during Panel business and deliberations, and that the meeting minutes would be prepared and certified by the Chair and be available to the public on the SAB website.

Dr. Vanessa Vu welcomed everyone to the meeting and thanked the Chair and Panel members for their time and willingness to serve on this important SAB review. She also thanked members of the public for submitting comments and noted that public comments are accepted throughout the review until completion. She urged the panel to consider public comments in their discussions and deliberations. She also acknowledged the presence of ORD representatives.

Review of Agenda

Dr. Buckley welcomed the review panel and asked panel members to introduce themselves. He stated that the purpose of the meeting was to vet key scientific issues, consider public comments, and discuss the preliminary responses to charge questions. He informed the panel of the process of the meeting. The lead discussants for each of the charge questions would first provide their comments followed by comments from other panel members. He emphasized that there would be additional opportunities for the Panel to further discuss these key scientific issues at the next face-to-face meeting to be scheduled in the fall.

Remarks from EPA's National Center for Environmental Assessment

Dr. Preuss thanked the SAB Panel for their review and provided an overview of EPA's process in the development of the Dioxin Assessment. He indicated that EPA's Dioxin Assessment started in 1990 at the request or the Administrator, and is now in its 21st years. The draft assessment(s) has been reviewed by the SAB four times. More recently, EPA received the National Academy of Sciences (NAS) review report in 2006. As EPA started to respond to NAS comments, the response to comment report evolved into something else. The process is as open as possible to gain input from the scientific community. For example, EPA performed a literature review and requested the public identify new studies. The Agency also convened a public workshop. Public comments received throughout the process are publicly available. Dr. Preuss noted that during 21

years, many dioxin experts have left the Agency. EPA expertise has become somewhat limited. He indicated that the report was prepared by EPA Scientists with input from outside experts. He underscored the need for practical advice from the SAB to improve the document which can be completed in the near term. He requested that the panel delineate needs for longer term work from near term recommendations. EPA does not plan to rewrite the 2003 document, but focus on pieces as appropriate to finalize the document. Dr. Preuss asked the Panel to focus on three areas which were recommended by the NAS in the revision of the Dioxin Assessment: (a) quantitative estimates of cancer risk; (b) uncertainty analyses; and (c) derivation of a Reference Dose (RfD) which was not done in 2003. He pointed out that it is the opinion of EPA scientists that a quantitative uncertainty analysis is not feasible at this time.

Dr. Preuss stated that other related areas, including toxicity equivalent factors, and remediation goals, are not subjects of the Dioxin Assessment and therefore should not be part of the SAB review. EPA's draft document was published in May, and the Agency will receive public comments through September. He indicated that the Administrator requested that the document be completed by December 2010.

In response to questions by panel members, Dr. Preuss clarified that the SAB is not asked to review the EPA 2003 draft assessment since the NAS has reviewed the document in entirety.

Public Comments

Dr. Buckley informed the panel and the audience that the SAB had received many requests from the public to make oral comments at the meeting. He stated that the list of registered public speakers and written public comments were available on the SAB website. He reminded the speakers to limit their presentations to 5 minutes. Public speakers were provided an opportunity to present their comments by phone or in person. Many speakers provided written oral statements which were made available during the meeting as well as on the SAB website. The order of public presentations was as follows:

- Dr. Olga Naidenko, representing Environmental Working Group (EWG) commented that EWG supports EPA's effort to finalize the dioxin assessment this year. Americans are exposed to dioxin. Until EPA completes its assessment, other government agencies and environmental cleanup efforts lack guidance to implement remediation measures critical to public health. EWG supports characterization of dioxin as carcinogenic to humans and urges SAB to support agency findings.
- Ms. Teresa Mills (on the phone), representing Environmental Network in Columbus, OH, commented that incinerators in Columbus which generate dioxin have created allergy and other health problems for residents in surrounding area. In 1994, a Dioxin public hearing was held for Ohio citizen. Sixteen years later, the Ohio citizens are still waiting for dioxin reassessment to be finalized. Ms Mills urged EPA to finalize dioxin document with no more delay.

- Dr. Lesa Aylward, of Summit Toxicology, representing Chlorine Chemistry Division of the American Chemistry Council (ACC) commented on EPA's derivation of RfD and Cancer Slope Factor. She stated that the PBPK model did not accurately reproduce the elimination of TCDD (Dioxin) in children, and EPA did not include non-TCDD TEQ in background. For cancer slope factor derivation, she commented that EPA chose the steepest regression coefficient from Cheng et al. (2006).
- Dr. Thomas Starr, of TBS Associates, representing the American Forest and Paper Association commented that three issues need to be addressed: the Emond et al. PBPK model is flawed; EPA's interpretation of Cheng et al. (2006) study is too narrow; and a comprehensive quantitative uncertainty analysis is absent in the document.
- Mr. Donald Hassig, of Cancer Action NY (on the phone) commented that any discussion of flaws and inadequacies of the draft dioxin reassessment merely serve to delay finalization.
- Mr. Mike Schade, of Center for Health, Environment and Justice presented a letter from individuals across U.S. who were exposed to dioxin. These individuals applaud EPA for finalizing the dioxin assessment and support characterization of dioxin as a known human carcinogen.
- Ms. Anna Gilmore Hall, Practice Greenhealth (on the phone) urged the SAB to expedite the review process to protect health and the environment. She thanked EPA for finalization of dioxin assessment and supported classification of dioxin as a known carcinogen.
- Ms. Michele Roberts of Advocates for Environmental Human Rights commented that residents from the Mossville, LA community were exposed to dioxin. The Mossville community is surrounded by seven industrial facilities that report dioxin releases in the Toxic Release Inventory. In 1998, EPA enlisted ATSDR to investigate dioxin exposure and found that dioxin in the blood of Mossville residents was three times higher than the national average.
- Ms. Laura Anderko, Alliance of Nurses for Healthy Environments, commented that in May 2009, she partnered with other health organization and wrote a letter to President Obama calling for release of the dioxin document. She said that she teaches people about how to protect themselves from dioxin and PCBs. She urged the SAB to meet EPA's 2010 deadline for release of the document.
- Dr. Janet Gray, Vassar College, representing the Breast Cancer Fund (on the phone), commented that the Breast Cancer Fund is concerned about the evidence that linked dioxin exposures to the development of breast cancer. She noted that dioxin is a cancer-causing agent that exerts its most powerful effects on later risk for breast cancer when people and animals are exposed early in life. She urged EPA to complete the dioxin document to protect American from this known carcinogen.
- Mr. Delmar Bennet, representing Mossville Environmental Action Now, Inc. commented that permits were given to plants which release dioxin in the air of the Mossville community. Workers do not realize they bring chemicals back to their family. In a survey in 1998, the Agency for Toxic Substances and Disease

Registry (ATSDR) found that residents in Mossville had dioxin levels in their bodies three times higher than the national average.

- Dr. Jay Silkworth, General Electric, commented that SAB should recommend that EPA refrain from applying dioxin risk values to PCBs unless or until the EPA implements the NAS recommendations relating to TEFs; and revises TEFs by incorporating more accurate estimates of human-specific relative potency of Dioxin Like Compounds (DLCs).
- Mr. Lewis Shepard, Cancer Action NY, commented on dioxin exposure for people who have to eat contaminated food and drink contaminated water. He urged that the debate be stopped and that action be taken to eliminate the problem.
- Ms. Lynn Thorp, Clean Water Action commented that the Clean Water Action supports the findings of the EPA report. She commented that the classification of dioxin as a known human carcinogen should no longer be a debate, and that there is no reason for further delay in finalization of the dioxin reassessment document.
- Dr. Robert Budinsky, Dow Chemical Company, representing the American Chemistry Council, discussed a mode of action model for TCDD-induced liver tumors and urged TEF issues to be part of the review process.
- Dr. John DeSesso, Exponent, representing Georgia Pacific, discussed evidence against the use of the Seveso cohort studies (Mocarelli et al., 2008; Baccarelli et al., 2008) as the bases for calculating the RfD, a chronic daily dose.
- Mr. Glen Silver, Concerned Citizens of Seneca County, NY, commented on a landfill that accepts incinerator ash and sewage sludge. He also commented on a state regulatory framework for incinerator ash, emphasized that contaminants can leach from buried ash in landfill to groundwater.
- Dr. John Doull, University of Kansas Medical Center (on the phone) posed three questions for the Panel's consideration:
    a. Did the EPA's document respond to NAS recommendation to use threshold basis for cancer assessment of dioxin?
    b. Did the Agency use best available data to reassess dioxin?
    c. What specific recommendations would you make to help the agency resolve the controversial issues associated with the risk assessment of dioxin?
- Ms. Carol Johnson, Ironbound Community Corporation (on the phone), commented on the impact of garbage incinerator and diesel truck traffic in the community and dioxin contamination in Passaic River. Ms. Johnson urged EPA to finalize the dioxin document.
- Dr. Devra Davis, Georgetown University, representing Environmental Health Trust, commented on the prolonged delay in completing the dioxin document. She pointed out that existence of scientific issues should not prevent the document from being released as final.

The meeting was recessed for lunch and was reconvened at 1:00 p.m. The Chair resumed the public comment session as follows:

- Mr. Rick Hind, Greenpeace (on the phone), commented on his concern about the never ending reassessment of dioxin, and the use of persistent pollutants in the Great Lakes area. He urged prevention of further dioxin contamination.
- Ms. Azita Mashayekhi, representing International Brotherhood of Teamsters, commented that the Teamsters union applauded EPA for finalizing and releasing the draft response to NAS report on dioxin. The final report will pave the way for NIOSH and OSHA to establish appropriate occupational exposure limits for dioxin. The Teamster union supports EPA's classification of dioxin as a known carcinogen, and urges EPA to meet its 2010 deadline for finalizing and releasing the dioxin reassessment.
- Dr. Michael Wolfson, representing Concerned Citizen of Onondago County (on the phone), commented on inadequate monitoring of dioxin released from an incinerator in the county. He also commented on the prolonged delay of the dioxin reassessment.
- Elizabeth Coker, Tennessean for Cleaner Environment (on the phone), commented on her son's allergic reaction to the PCB in his raincoat and boots. She commented that the public has the right to know about the adverse health effects of dioxin on children.

Discussion of Responses to EPA's Charge Questions

Section 2- Transparency and Clarity in the Selection of Key Data Sets for Dose-Response Analysis

Dr. Buckley asked the lead discussants to comment on this section of the document. Panel members generally found this section responsive to the NAS concern about transparency and clarity in data set selection. Members found study inclusion criteria to be clear, although exclusion criteria for animal studies and mechanistic studies can be more clearly provided. A justification is needed for the requirement for the purity of administered dioxin used in a study. Some panel members suggested that perhaps the study exclusion rationale may be provided by adding a column in the table in the document, e.g,. dose or purity did not make the cut. The choice to exclude studies of Dioxin Like Compounds (DLCs) was not fully supported by all members.

Some panel members expressed concern about not including TEQ in the evaluation. Dr. Preuss explained there is a separate EPA effort on TEQ. The Panel asked EPA staff to explain how EPA determines if an effect is adverse, and commented this should be clarified in the beginning of the document. Dr. Buckley summarized the discussion as follows:

- In general, EPA was responsive to NAS. There are some suggestions for more transparency and clarity;
- The process for data selection is clearly defined;
- There are some issues with how a study is excluded; and
- The Panel asked EPA to define what is an adverse effect.

Section 3- The Use of Toxicokinetics in the Dose-Response Modeling for Cancer and Noncancer Endpoints

The lead discussants expressed support for the use of whole blood concentration for dose-response assessment rather than body burden. There was some discussion about the appropriateness of the use of whole blood concentration since the issue is dose-dependent distribution of dioxin with CYPA1 induction, and concentration is dose-dependent. Use of whole blood concentration is a good representation of free concentration. Use of whole blood concentration vs. lipid-adjusted serum concentrations as a dose metric will not greatly impact risk, but is a variation of representation. Panel members also supported the use of the Emond et al. PBPK model for dose metric calculations. There was discussion about the need to strengthen the rationale for the exclusion of models. The Hill parameter is the most sensitive parameter in the model, which is a source of uncertainty in risk assessment. The clearance rate for children is an uncertainty issue. There are dynamic windows of susceptibility during fetal development, and these cannot be addressed by PBPK model.
Although the Hill parameter is the most sensitive parameter in the model, it was left out of the sensitivity analysis in EPA's document. Sensitivity analysis for this parameter can be conducted. Panel members also commented that something can be done to characterize model uncertainty.

Dr. Buckley summarized key points of discussion as follows:

- In general, the Panel agreed with the PBPK model approach and the use of whole blood concentration as dose metric.
- The Emond et al. model is the right way to go, but there are some limitations.
- The Hill coefficient and clearance in children are sensitivity issues.

Dr. Armitage, the DFO, adjourned the meeting approximately 5:00 p.m.

July 14, 2010

The meeting was reconvened at 8:35 a.m. Dr. Buckley asked Dr. Clewell to provide a synopsis of the panel's discussion on section 3 of the document on the previous day. Dr. Clewell read his written comments as follows:

There was an agreement on the use of whole blood concentration as a dose metric. The discussion of how to model lipid-adjusted serum concentrations is not clear in EPA's document. The panel endorsed the Emond et al. model. Model modification made by EPA is appropriate. There was a good qualitative uncertainty analysis in the document, however, it could be more quantitative in model prediction. The Hill coefficient, as pointed out by Dr. Tom Starr (a public speaker), can bring about orders of magnitude

difference in Monte Carlo propagation, which can be characterized in uncertainty analysis. The Model performed well. The mouse model performed well also. The Model provides useful way to estimate internal exposure. The Hill coefficient was not included in sensitivity analysis, and it is the most sensitive parameter.
Dr. Buckley then asked the panel to move on to the discussion of section 4 of the document.

Section 4- Reference Dose

The lead discussants expressed support for the use of Baccarelli et al.(2008) and Mocarelli (2008) as critical studies for the derivation of the RfD. They found that the endpoints were well justified, but the rationale for selection should be strengthened, and these studies should be integrated into the bigger picture of epidemiology studies and animal studies. There was discussion indicating that the selection of sperm endpoint and thyroid endpoint is relevant to real world exposure. While elevation in TSH blood level in neonates and 20% decrease in sperm count were not clear cut in clinical terms, they do represent changes in function. Early windows of susceptibility are the most critical period of exposure, and there is strong basis for using these two studies since they focused on early life exposure. The Panel also discussed the use of animal bioassays and supported the comparison of the RfD array derived from human studies and animal bioassays. This showed the high degree of similarity. Dr. Glen Rice from EPA indicated that at EPA's dioxin workshop, there was strong push for using human data for RfD derivation.

Panel members commented that the criteria for strengths and limitations in Table 4-6 of the Agency's document were not well defined. Establishing criteria for strengths and limitations upfront would be informative. Mouse bioassay data were thrown out without strong justification. The Panel discussed whether biochemical changes/endpoints (e.g., CYPA1 induction, oxidative stress parameters) should be included for evaluation. There was some discomfort among panel members that there were sensitive endpoints that had not been included in the table. There was a comment that BMD modeling to the point of departure (POD) is appropriate but should not be modeled below the POD. There was a comment that there is a need for a better discussion of the uncertainty factor, especially the discussion concerning not using a data quality uncertainty factor.

The panel recessed for lunch and the meeting was reconvened at 1:15 p.m. Dr. Buckley asked the panel to move on to the discussion of section 5.

Section 5- Cancer Assessment

The Panel discussed EPA's weight of evidence cancer classification for Dioxin. The panel asked for information about EPA's Cancer Guidelines. Following Dr. Vu's explanation of EPA's criteria for classification, the majority of the panel supported EPA's conclusion (in accordance with EPA's cancer guidelines) that TCDD (Dioxin) is a human carcinogen. One panel member commented that TCDD is not a human carcinogen at environmental exposure levels.

The panel asked if the power of detection for all cancer or specific cancer was delineated, in EPA's draft assessment. EPA staff indicated that power was not discussed. One panel member suggested that EPA look at the power of detection for rare tumors in negative studies. It was suggested that homework for discussants would be to look at the discussion of evidence in section 5 that supports classification and to consider how to enhance this discussion. The panel then discussed the mode of action of TCDD. There was a comment that for lymphoma, one still does not know if the Ah receptor is involved in the pathway. There was a question to EPA focusing on why apoptosis was not included in the MOA discussion. Dr. Hawkins responded that a more detailed discussion of the mode of action was provided in EPA's 2003 document which covered apoptosis. It was noted that the current EPA's document is a supplemental document, not a stand alone document.

The panel recommended that the data selection discussion presented in section 2 should be carried forward to section 5 along with the rationale for data selection for dose-response assessment. A suggestion was made to add a column in Table 2-4 to explain why the studies (presented in table 5-1) were selected for estimating cancer risk.

The panel expressed general support for EPA's selection of the appropriate animal bioassays for dose-response assessment of cancer risk, the choice of a $BMDL_{01}$ as the POD, and the use of the Cheng et al. (2006) epidemiological study as the critical study for oral slope factor development. The panel commented that the Emond PBPK model is appropriately applied, and that the use of log linear relationship of fat concentration and rate ratio to estimate risk-specific doses was the appropriate extrapolation approach.

The panel expressed different views on whether DLCs should be included in cancer dose-response modeling. EPA representatives commented that Table 2-1 has some information on TEQ in some studies. A homework assignment was made to one Panel member to further address this issue. There were also different opinions expressed about the use of non-linear approach for the assessment of TCDD carcinogenicity and on whether it is appropriate to ask EPA to do more work to address this issue.

The Chair informed the Panel that the discussion of uncertainty analysis would be postponed until the next morning. He asked the lead writers to develop a synthesis of the panel discussions of the responses to EPA's charge questions and to be prepared to present these to the panel in the morning of the next day. The meeting was adjourned at approximately 5:00 p.m.

July 15, 2010.

The panel reconvened at 8:35 a.m. The Chair asked the lead discussants on Section 6 to present their comments.

Section 6- Uncertainty Analysis

The panel generally found that the section is clearly written although the write-up can be more reader friendly, so that non-statisticians will be able to read this section. There was considerable discussion about EPA's decision not to perform a quantitative uncertainty analysis. Many members indicated that it is essential for EPA to conduct some types of sensitivity analyses to respond the the NAS recommendations. The Panel discussed whether a comprehensive quantitative uncertainty analysis is feasible. Some members commented that many analyses had already been done, and noted that a compromise approach could be used to address uncertainty. Various approaches were discussed. These approaches included: Monte Carlo analysis (it was noted that this is not practical because the distribution is not known), bounding approaches, value of information approach, info-gap, decision tree (which needs expert elicitation). The Panel commented on the need to change some terminology in EPA's document: "exotic model" and"volitional uncertainty". The Panel would like to suggest an uncertainty analysis approach that could be accomplished.

Dr. Roger Cook (EPA's consultant who is the author of Section 6) responded to panel comments and explained the definition of quantitative analysis in the document, and the decision not to use an expert judgment, value of information approach. Dr. Peter Preuss commented that uncertainty analysis will not be particularly helpful. He noted that some value of information methods have been done by EPA. More often, it demonstrates the obvious, i.e. that different people have different opinion. There is no point to do uncertainty analysis just for the sake of uncertainty analysis. At the end of the discussion, the Panel generally agreed that expert elicitation is not feasible because of time and budget constraints.

The Chair then asked the Panel to move to the next agenda item, summary of discussion.

Summary of the Discussion

The Chair asked the lead presenters to provide a summary of their assigned sections. This was followed by additional comments from other lead writers and a short discussion from other panel members. The following summaries captured the key points made by the lead discussants and panel members

Section 2- Drs. Lawrence, Persky

- Overall, there were many strong aspects regarding the thoroughness and clarity of this section.
- There is a need for greater clarity on study exclusion.
- Careful editing of the document is needed.
- Overall document integration can be improved so that it is easier to follow a study from one section of the document to another.
- The data selection criteria for should be included in tables or stated briefly at the beginning of each section.

- The limitations of narrow selection of just a few studies are a concern. A recommendation was made that the rationale for exclusion of a study be added to Table 2-7 to make this process more evident to the readers.
- The rationale for selection criteria for epidemiological and animal studies should be made stronger.
- There is no consensus regarding the scientific justification for some of the inclusion and exclusion criteria. Perhaps EPA may have been too stringent in exclusion of some excellent studies. Adding information to the appendices and/or tables regarding exclusion of particular studies would be helpful.
- While panel members have identified additional studies, it was not clear whether including them would have a significant impact on the dose response assessment.
- Some phrases, e.g. "study design is consistent with standard toxicological practices" need clarification.
- The weight of evidence given to null studies could be given in more detail, particularly for epidemiological studies.
- EPA should provide a more expanded rationale for their definition of adverse health effects.

Section 3- Drs. Clewell and Fisher

- The use of body burden in 2003 was an improvement over the use of administered. However, the use of whole blood concentration is better than body burden since it is more closely related to biologically relevant dose metric, and is endorsed by the panel.
- The Emond et al. model provides the best available basis for dose-metric. However, additional discussion of other published models and quantitative evaluation of the impact of model selection on dose metric predictions should be provided.
- The discussion should address how the model is used in the assessment, which would then dictate why a particular model was selected.
- Modifications made by EPA to the published Emond et al. model are minor, and appropriate.
- EPA conducted a thorough qualitative uncertainty analysis, but a more quantitative uncertainty analysis is needed, using Monte Carlo techniques. It is critical to demonstrate the dependence of Human Equivalent Dose (HED) and risk predictions on uncertainty and variability in the model parameters, particularly those with high uncertainty.
- The Agency did a good job on the mouse model. However, the model should be externally peer reviewed.
- The mouse model performs well, apart from under-prediction of urinary excretion.
- The modified Emond model performs well in estimating human exposures on the basis of internal exposure measurements. Nevertheless, there is considerable uncertainty associated with attempting to reconstruct prior exposures in a human population.

- Sensitivity analysis is not adequate in the EPA document. It leaves out the Hill coefficient, which is one of the most important parameters in the model for low-dose extrapolation.
- The average daily dose calculation approach is appropriate. There was some concern for developmental application, so sensitivity analysis can be conducted for different age.

Section 4- Drs. Faustman and Petersen

- The Panel supported the use of the Baccarelli et al.(2008) and Mocarelli (2008) as critical studies for the derivation of the RfD.
- The Panel recommended that the animal studies and epidemiologic studies should be more integrated.
- The panel had concern about EPA's definition of adversity. Adversity should be considered differently for developmental endpoints from general toxicity.
- Criteria for strengths and limitations in Table 4-6 were not well defined. Establishing criteria for strengths and limitations upfront would be informative.

Section 5- Dr. Håkansson

- The Panel generally agreed on EPA's classification that TCDD is carcinogenic to humans. However, it was noted that one member had a dissenting view that TCDD is carcinogenic at high doses but not at current environmental exposure levels.
- There is need for more information from the Agency on the power of the studies used and the difficulties involved when assessing rare tumors.
- EPA should thoroughly address these issues to make the hazard characterization more clear and transparent.
- An updated discussion of TCDD mode of action vs. mechanism of action is needed for different health endpoints, including life-stage sensitivity issues.

Section 6- Presenter: Drs. Ferson and Small

- The panel commended EPA for the effort but recommended the Agency to extend the sensitivity analyses to fully respond to the NAS recommendations.
- There are many ways to do quantitative uncertainty analysis without conducting an expert elicitation study.
- Bounding analysis is an uncertainty analysis. Possible bounding approaches include: interval analysis, nesting of intervals, info-gap decision theory, probability bounds analysis.
- Model uncertainty, including uncertainty about dependencies, can also be addresses with bounding approaches.

Next Steps

Dr. Buckley thanked the panel for their active participation. He acknowledged that there is additional challenging work ahead in preparation for the next face-to-face meeting in the fall. He asked Panel members to update their preliminary comments in a month. In addition, the Lead writers were asked to provide written summary of discussion to DFO in a month in the way it was presented.

Dr. Preuss and Dr. Vu thanked the panel, and meeting was adjourned at approximately 2:15 p.m.

Respectfully Submitted:	Certified as True:
/signed/	/signed/
Diana Wong, Ph.D., DABT Designated Federal Officer	Timothy Buckley, Ph.D. Chair

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by panel 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 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

U.S. Environmental Protection Agency
Science Advisory Board
Dioxin Review Panel

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