

**Summary Minutes of the  
US Environmental Protection Agency  
EPA Science Advisory Board  
Dioxin Review Panel  
Public Meeting  
October 27-29, 2010**

**ATTENDANCE**

SAB Panel Members

Dr. Timothy Buckley (Chair)  
Dr. Harvey Clewell  
Dr. Louis Anthony (Tony) Cox  
Dr. Elaine Faustman (by phone)  
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

SAB Staff Office

Dr. Vanessa Vu, Director  
Dr. Thomas Armitage, Designated Federal Officer (DFO)  
Dr. Diana Wong, Designated Federal Officer (DFO)

EPA's National Center for Environmental Assessment (NCEA)

Rebecca Clark, Acting Director  
Dr. Glenn Rice  
Dr. Jeff Swartout  
Linda Teuschler  
Linda Tuxen

Other Attendees (with their affiliations as entered on the sign-in sheets)

Dr. Hisham El-Masri, EPA, ORD  
Bob Budinsky, Dow Chemical  
Thomas Starr, TBS Associates  
Lesla Aylward, Summit Toxicology

Roger Cooke, RFF  
Jay Silkworth, GE  
David Fisher, ACC  
Dale Hattis, Clark University  
Resha Putzrath, Navy  
Paul Villeneuve, Risk Sciences  
Pat Casano, GE  
Claude Emond, U. of Montreal  
Scott Bartell, University of California  
Cheryl Hogue, C & E News  
Maria Hegstad, Inside EPA  
Marcus Cooke, CCT  
Mark Lee, ICF  
Audrey Turley, ICF  
James Lamb, Exponent  
Nancy Beck, OMB  
Craig Barren, Consultant  
Olga Naidenko, EWG  
Laurie Holmes, ToxStrategies  
Mark Harris, ToxStrategies  
Sarah McCallen, ACC  
Azita Mashayekhi, International Brotherhood of Teamsters  
Alan Korski, BNA  
Alicia Oman, NAM  
Kenneth Mundt, Environ  
John Schell, Entrix  
Richard Krock, Vinyl Institute  
Gregory J. Bacchi, Vinyl Institute  
Robert Scheuplein, Keller Heckman  
Marlene Berg, USEPA  
Gail Charnley, Health Risk  
Brian Magee, Arcadis  
Mike DeVito, NTP/NIEHS  
Sarah Opperman, Opperman Consulting  
Sonja Kavac, ACC  
Matt Lorber, USEPA  
Burbesor Smitz, PNG  
Laura Ford Brust, Sullivan & Worcester

## **MEETING MATERIALS**

The following meeting materials were available prior to or during the October 27-29, 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/91bf4b5a068396048525779d006e7bf6!OpenDocument&Date=2010-10-27>

- 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)
- AGENCY BRIEFING MATERIAL
  - Presentation by Glenn Rice “The U.S.EPA’s Draft Oral Slope Factor (OSF) for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)”, (PDF, 13 pp., 199, 153 bytes)
  
  - Presentation by Jeff Swartout on “The U.S. EPA’s Draft Oral Reference Dose (RfD) for 2,3,7,8-Tetrachlorodibenzo-p-dioxin(TCDD)”, (PDF, 11 pp., 97,642 bytes)
  
  - Presentation by Linda K. Teuschler on “The Application of Study Selection Criteria to TCDD Epidemiologic Studies and Animal Bioassays for Development of a Reference Dose and Cancer Oral Slope Factor”. (PDF, 18 pp., 176,972 bytes)
- AGENCY FOLLOW-UP
  - Material provided by EPA in response to questions from the SAB regarding the limitations of bounding analyses in quantitative uncertainty analyses. (PDF, 5 pp., 98,461 bytes)
  
  - Revised Table 5-21 in EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments. (PDF, 1 pp., 115,229 bytes)
- PUBLIC COMMENTS
  - Comments from James J. Collins, Dow Chemical Company. (PDF, 4 pp., 19,069 bytes)
  
  - Comments from John Doull, University of Kansas Medical Center. (PDF, 25 pp., 827,666 bytes)

Comments from Joseph Haney, Texas Commission on Environmental Quality. (PDF, 8 pp., 165,998 bytes)

Comments from Judith Nordgren, Chlorine Chemistry Division, American Chemistry Council. (PDF, 8 pp., 476,214 bytes)

Comments from Olga Naidenko, Environmental Working Group. (PDF, 4 pp., 142,137 bytes)

Comments from Walter Shaub, U.S. Chamber of Commerce. (PDF, 2 pp., 63,659 bytes)

Comments from W. Marcus Cooke, Cooke Companies International. (PDF, 2 pp., 90,590 bytes)

List of public speakers. (PDF, 4 pp., 32,677 bytes)

Presentation from Brian Magee, ARCADIS, U.S., Inc. (PDF, 8 pp., 455,035 bytes)

Presentation from Gail Charnley, Health Risk Strategies. (PDF, 6 pp., 282,387 bytes)

Presentation from Jay Silkworth, General Electric Company. (PDF, 8 pp., 317,096 bytes)

Presentation from Kenneth A. Mundt. (PDF, 5 pp., 91,717 bytes)

Presentation from Laurie Haws, ToxStrategies Inc., on behalf of U.S. Magnesium (PDF, 6 pp., 1,801,760 bytes)

Presentation from Lesa Aylward, Summit Toxicology, on behalf of the American Chemistry Council. (PDF, 10 pp., 420,732 bytes)

Presentation from Lorenz Rhomberg, Gradient. (PDF, 5 pp., 40,751 bytes)

Presentation from Mark Harris, ToxStrategies Inc., on behalf of Terra Solutions Inc. (PDF, 6 pp., 629,779 bytes)

Presentation from Robert A. Budinski on behalf of the American Chemistry Council. (PDF, 8 pp., 256,947 bytes)

Presentation from Thomas B. Starr, TBS Associates, on behalf of the American Chemistry Council. (PDF, 6 pp., 646,125 bytes)

Statement from Stephen Lester, Center for Health, Environment, and Justice.  
(PDF, 2 pp., 107,635 bytes)

Public comment transmitted EPA Docket Comments, October 12, 2010. (PDF, 9 pp., 203,810 bytes) through the EPA docket.

## **PURPOSE**

The SAB Dioxin Review Panel held the second face-to-face meeting to continue 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 responses to EPA's charge questions.

## **LOCATION**

Park Hyatt Washington Hotel, 1201 24<sup>th</sup> Street. NW, Washington, D.C. 20037

## **DATE AND TIME**

The meeting was held on October 27, 2010 from 9:00 a.m. to 5:25 p.m. (Eastern Time), October 28, 2010 from 8:30 a.m. to 5:00 p.m. (Eastern Time), and October 29, 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.

### **Wednesday, October 27, 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 require that all meetings where discussions and deliberations take place must be held in public. He noted that the SAB Panel members were 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. Vanessa Vu, Director of the SAB Staff Office, welcomed everyone to the meeting and introduced Becki Clark, Acting Director of NCEA, and the DFOs Dr. Thomas Armitage and Dr. Diana Wong.

#### 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 continue deliberation on responses to EPA's charge questions. Dr. Buckley also described the agenda of the meeting.

#### Remarks from EPA's National Center for Environmental Assessment (NCEA)

Ms. Becki Clark, Acting Director of NCEA, welcomed SAB's robust review of the dioxin report. She mentioned that the dioxin exposure study (9/2009) and the State Soil Cleanup Level report (12/2009) were posted on EPA's website. Ms. Clark also mentioned other EPA activities on dioxin: OSWER's work on preliminary remediation goals and the EPA Risk Assessment Forum's draft dioxin TEFs. These activities are not the subject of this review. Ms. Clark then acknowledged authors outside EPA who contributed to the dioxin assessment. She clarified that EPA was looking for advice to improve the document in the short-term, and not looking for a long-term research agenda.

#### EPA Presentation:

- Ms. Linda Teuschler presented the application of study selection criteria to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) epidemiologic studies and animal bioassays for development of a reference dose and cancer oral slope factor. All available peer-reviewed epidemiologic studies on TCDD through October 2009 were evaluated using 5 considerations. For animal bioassays, studies were evaluated based on three considerations.
- Dr. Jeff Swartout presented EPA's derivation of the draft oral RfD for TCDD. A large number of laboratory animal dose-response data were available for dose-response assessment. Monkey studies showed high serum dioxin-like compounds (DLCs) levels, and therefore did not satisfy the criteria for inclusion. Dr. Swartout also explained the toxicological relevance of the inclusion criteria. By policy, an adverse effect does not have to show immediate clinical effects, and is defined as "... a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge." For human data, the focus was on the Seveso study, which involved developmental and reproductive endpoints. Candidate RfDs derived from human studies were in the middle of range of candidate RfDs derived from animal bioassays. Human epidemiologic data was selected over rodent bioassay data.
- Dr. Glenn Rice presented EPA's derivation of draft oral slope factor for TCDD. According to EPA 2005 cancer guidelines, linear extrapolation is appropriate when an agent has a mutagenic mode of action or acts through another mode of action expected to be linear at low doses, or when data do not establish the mode of action. Nonlinear extrapolation is appropriate when there is no evidence of linearity, and when information is sufficient to support a mode of action that is nonlinear at low doses. EPA identified candidate cancer OSFs from 4

epidemiological cohorts showing associations between TCDD and increased cancer or cancer mortality risk: NIOSH, Hamburg, BASF, and Seveso. EPA identified candidate cancer OSFs from 5 animal bioassays. EPA chose OSFs derived from the human data over the animal data as recommended by the panelists at EPA's 2009 dioxin workshop.

### Public Comments

Dr. Buckley informed the Panel and the meeting attendees 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 at the meeting and posted on the SAB website. Public commenters presented in the following order:

- Mr. Donald Hassig, of Cancer Action NY (on the phone) encouraged EPA to complete the Dioxin reassessment and expressed his views concerning comments that had been provided to the Panel.
- Dr. Jay Silkworth, General Electric, commented on species sensitivity differences in humans and rats. Current WHO TEFs are derived from rodent studies. NAS (2006) recommended adjusting for species sensitivity differences if evidence is available. Some *in vitro* data on human cells are available and indicated human cells are less sensitive than rhesus monkey and rat cells.
- Dr. Lesa Aylward, Summit Toxicology, representing American Chemistry Council, (ACC) commented on pharmacokinetic modeling and the derivation of reference doses in the mode of action analysis. Dr Aylward commented on quantitative issues in toxicokinetic modeling, application of interspecies toxicodynamic uncertainty factors, and non-reproducible values in Table 5-21, Illustrative RfDs based on hypothesized MOAs for liver and lung tumors.
- Dana Patterson, (on the phone), Edison Wetlands Association of New Jersey, commented that dioxin is unsafe for human health. Dioxin is in superfund sites. It is a human carcinogen, and has wide range of noncancer effects. She urged EPA to meet the 2010 deadline.
- Dr. Kenneth Mundt, ENVIRON, commented on TCDD and cancer, based on his review of epidemiological evidence with co-authors. In 1997, IARC concluded dioxin has "limited" evidence for humans based on overall increase in risk of "all cancers". In 2009, IARC concluded "sufficient" evidence for humans, based on evidence for "all cancers" combined. Updates supportive of a positive association include dose-response or lagged analyses of US herbicide manufacturers, and updated mortality follow-up Seveso studies. Updates failing to support a positive association include SMR analysis of US herbicide manufacturers, cancer incidence data from Seveso, mortality update of Dutch herbicide manufacturers, and Vietnam veteran studies. Dr. Mundt concluded that while the hypothesis that TCDD is a human carcinogen is plausible based on experimental evidence, in

their opinion, the weak and contradictory evidence from epidemiological studies failed to conclusively demonstrate a causal association.

- Stephen Lester, Science Director for Center for Health, Environment & Justice (CHEJ), expressed concern for the public exposed to dioxin. He offered comments on three specific areas: 1) Transparency and clarity in the selection of key data sets; 2) Cancer risk assessment; and 3) the reference dose. CHEJ found that EPA's Reanalysis of Key Issues related to Dioxin Toxicity and Response to NAS comments provided the transparency and clarity on EPA positions that the NAS has requested. CHEJ supports and commends EPA's determination that TCDD is carcinogenic to humans, supports derivation of oral slope factor based on epidemiologic study, and the linear non-threshold dose response model to estimate cancer risk. CHEJ believes the rationale for the selection of male reproductive effects (Mocarelli et al., 2008) and changes in neonatal thyroid hormones levels (Baccarelli et al., 2008) as co-critical effects to derive a reference dose (RfD) for TCDD was clearly described and scientifically justified. However, CHEJ was concerned that the derived RfD did not take into account the unique susceptibility and vulnerability of children. CHEJ urged EPA to finalize the dioxin assessment and protect the health of the American people.
- Monica Wilson, of Global Alliance for Incinerator Alternatives, a global network of 65 countries. Ms. Wilson urged EPA to meet the deadline for the dioxin reassessment. People in 65 countries cannot afford to wait.
- Dr. Gail Charnley, HealthRisk Strategies, commented that: 1) EPA failed to follow its own risk assessment guidelines and the NAS for weight of evidence analysis, and selected only studies that demonstrated a positive result and dose-response relationship; 2) There was no demonstrated clinical significance of noncancer effects chosen for RfD.
- Dr. Lorenz Rhomberg, Gradient, commented that EPA's conclusion for insufficient evidence to support a nonlinear dose-response for TCDD is contrary to the conclusion of the NAS Panel reviewing the 2003 document, and EPA's own guidance for criteria for conducting nonlinear assessments. Dr. Rhomberg commented that the key features of MOA for TCDD, AhR mediation, are established, and that receptor-mediated effects are widely expected to have thresholds. Several EPA guidance documents mandate forthright exploration of alternatives even if less-than-absolute support. Choice is a risk management decision.
- Dr. Thomas Starr, TBS Associates, on behalf of ACC, commented that the Emond et al. PBPK model exhibits problematic supralinear behavior at low doses ( $n=0.6$ ). He recommended that the Emond et al. PBPK model be dropped, and use CADM for cancer and noncancer endpoints. He also recommended that smoking and exposures to workplace carcinogens other than TCDD be addressed; and that USEPA should implement a threshold-based approach to cancer risk assessment.
- Dr. James Collins, Dow Chemical Company, commented that Dow epidemiologists conducted the first cohort mortality study on trichlorophenol workers exposed to TCDD, and have updated this original cohort mortality study four times over the past 30 years. Exposure assessment has been improved

through the use of serum dioxin measurements on a sample of exposed workers. Other than chloracne and possibly soft tissue sarcoma, no health effects have been found to be related to TCDD. Dow scientists also completed a study of former trichlorophenol workers at a Dow site in New Zealand with a university group, and concluded there was no increased risk of any cause of death related to dioxin exposure. He concluded that Dow's experience with its studied populations of exposed workers did not support EPA's conclusions that TCDD is carcinogenic in humans.

- Dr. Mark Harris, ToxStrategies, on behalf of Tierra Solutions, commented that: 1) the NIOSH cohort may have confounding exposures other than TCDD; 2) NIOSH cohort exposure estimates were based on a job exposure matrix that was subjective and qualitative, actual measurements of TCDD serum concentrations were limited to 170 of 3,538 workers; 3) the critical noncancer effects selected by EPA were not clinically significant, and not appropriate; and 4) the draft RfD and oral slope factor (OSF) suggest that the U.S. food supply may be unsafe for human consumption.
- Dr. Laurie Haws, ToxStrategies, on behalf of U.S. Magnesium, commented on the debate about linear vs non-linear approaches for cancer and different approaches for developing non-cancer toxicity benchmarks. EPA OSF- based TEQ serum concentrations were below the NHANES detection limit. EPA OSF and RfD would result in serum concentrations below background. If EPA derived values are applied, people are at risk at background levels.

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

- David Tundermann, U.S. Magnesium, commented that lower soil dioxin concentrations do not translate into lower dioxin serum levels. Moreover, lifetime exposure to dose based on EPA OSF and non-cancer reference dose would result in serum concentrations well below background. If EPA is correct, everyone is at risk. U.S. Magnesium conducted blood sampling of some workers in 2005 and found that blood levels of dioxins and furans were below levels associated with observable health effects. He noted that the EPA derived OSF and RfD could alarm workers about exposure to dioxin, and there could be unfortunate economic consequences.
- Laura Anderko, Georgetown University Alliance for Health, concluded that EPA has fully addressed NAS concerns. She commented that studies in children show adverse health effects of TCDD in long term exposure. She urged EPA to release dioxin reassessment to meet 2010 deadline.
- Dr. Olga Naidenko, Environmental Working Group (EWG), commented that EWG supported the EPA reassessment. EPA's table of proposed RfDs showed the RfD proposed by EPA is at the midpoint of the candidate RfD array derived by EPA from a wide range of animal toxicity studies. This RfD demonstrated EPA used a moderate approach. Dr. Naidenko commented that the opposition to EPA's dioxin assessment contains spurious arguments. EWG confirmed that infants and young children ingest more dioxins from food, relative to their body

weight, than any other segment of the population. Exposure to dioxin from food, and in breast milk is a fact of life. EWG urged the SAB review panel to support EPA in its efforts to complete the process and issue final standards.

- Charlotte Wells, Galveston Baykeeper (on the phone), commented there was an advisory for limited consumption of trout in Galveston bay. Two years ago, waste from a paper company was found in a pit, and it became identified as a Superfund site. The proposed remedy for the pit traced back to water in Galveston Bay. She commented that strong coordinated EPA and industry effort is needed. She noted that once dioxin is in the body, it will accumulate in fat tissue. She urged site cleanup.
- John Doull, U. Kansas Medical School, commented that many issues the SAB dioxin review Panel were reviewing have been addressed by other groups. Dr. Doull commented that the Hercules petition to the U.S. Supreme Court, on behalf of 31 distinguished scientists, asked EPA to justify the linear extrapolation approach. He also commented on the economic effects of regulation. The Panel Chair asked if Dr. Doull suggested EPA misapplied the cancer guideline. Dr. Doull responded by indicating that if EPA uses the linear approach, the threshold approach should be used side by side. (Dr. Doull was a member of the Hercules group, and spoke as individual.)
- Robert Scheuplein, consultant to Keller and Heckman, commented that he has clients impacted by the dioxin reassessment. WHO calculated acceptable levels to be 2.7 pg/kg/month. EPA derived values are 3 orders of magnitude lower than other countries.
- David Garabrant, U. Michigan, (on the phone), commented that his research on serum dioxin levels found no relationship between dioxin concentration and serum dioxin concentration. Weak associations were found between serum and household dioxin level. His studies also found no association between serum concentration and soil contact and soil ingestion. Soil concentration at 1000 ppt has no effect on serum dioxin concentration.
- Joseph “Kip” Haney, Texas Commission on Environmental Quality (TCEQ), commented that the cancer-based new preliminary remediation goal (PRG) will be over 150 times lower than current PRGs at 1E-5 excess risk level. Using the draft RfD, the Maximum Contaminant Level (MCL) will be much lower. Mr. Haney also commented that average adult and child intake may exceed the draft RfD, especially for children, which may raise public concerns about the safety of the US food supply. Also, if the draft RfD is used, breast feeding will not be recommended. He commented that it is important to follow NAS recommendations for the nonlinear approach which will result in an acceptable dioxin intake level of 10 – 100,000 times higher.
- Ken Horn, State Representative, Michigan House of Representatives, (on the phone), commented that dioxin became a household word in his region, and the region has dealt with cleanup for a long time. At 90 ppt, Michigan maintains one of the strictest cleanup standards for dioxin, and the current EPA site-specific standard made more sense. He mentioned that results of a human exposure study by University of Michigan and Michigan State University study on animal wildlife exposure were forthcoming. He expressed concern about a cleanup

standard change from dioxin assessment. He commented that the dioxin cleanup goal selected by EPA should be fully reviewed by the scientific community, and that rules not be changed again one more time.

- Dr. Brian Magee, Arcadis, commented that the proposed oral slope factor (OSF) was based on estimated TCDD exposure and ignored all other dioxins and furans. The OSF was overestimated and overpredicted observed cancer mortality. EPA has not validated the proposed OSF, and preliminary screening validation showed that proposed OSF was not realistic. He also commented that the proposed RfD from Mocarelli et al. (2008) and Baccarelli et al. (2008) were flawed, and that the proposed RfD over-predicted observed effects on thyroid and male reproduction.
- Beverly Smiley, Solutions Through Science, commented that the EPA dioxin reassessment did not follow NAS recommendations. EPA rejected uncertainty analysis that is the corner stone of the assessment. She indicated that the SAB should welcome EPA adopt a weight of evidence approach and a non-linear approach.
- Dr. Walter Shaub, U.S. Chamber of Commerce, (on the phone), commented that the Agency's dioxin assessment is a matter of great importance and that all possible effort should be undertaken to develop an assessment that is balanced, comprehensive, transparent, reflects the most recent peer reviewed knowledge, and is defensible.
- Rich Krock, The Vinyl Institute, commented that his parent's home is near an incinerator that generated dioxin. A coal burning plant was about 2 miles from his parent's house. He commented on the longevity of his parents' lives, although the family ate fruits and vegetable from the backyard. He had been exposed to high level of dioxin, yet he has not developed adverse health effects. He urged EPA to use weight of evidence approach.
- Dr. Robert Budinski, Dow Chemical, on behalf of ACC, commented that EPA incorrectly rejected the MOA for dioxin carcinogenicity, and failed to follow their own MOA framework in 2005 cancer guideline. He commented that a workshop on Dose-Response Approaches for Nuclear Receptor-Mediated Mode of Action was held on September 27-29, 2010 at NIEHS in Research Triangle Park, NC. An expert panel dedicated to examine the MOA, key events, and dose-response relationships for important nuclear receptors was able to derive a MOA for dioxin-promoted rodent liver tumors.
- Ms. Azita Mashayekhi, Industrial Hygienist, International Brotherhood of Teamsters, commented that the workers in the Teamsters union are engaged in solid waste and hazardous waste collection. The Teamsters union is very interested in the dioxin assessment. Dioxin in landfill fires is of concern. Dioxin and furans in landfill fires contributed to 25% or more of dioxin released. NIOSH is about to conduct a new 8 plant study. NIOSH questioned the exclusion of the Ranch Hand Study. NIOSH also suggested that EPA look at Warner et al. because it involved a single exposure study.
- Alicia Oman, National Association of Manufacturers, commented that EPA reanalysis of dioxin is of concern to their members. Scientific analysis should include cost benefit analysis. Manufactures believed EPA must use the latest science, and that EPA has not looked at cleanup cost.

- James Lamb, Exponent, on behalf of Georgia Pacific, commented on the design of the Mocarelli et al. (2008) study and that sperm quality is a highly variable endpoint. The mean sperm count was in normal range. He questioned if hormones were correlated with sperm counts and if the study defined the critical effect.
- David Fischer, Assistant General Council for ACC, commented that EPA did not adequately address the NAS comments. He commented that EPA had not used a weight of evidence analysis; and that EPA should revise the 2003 reassessment into a stand alone document. Mr. Fischer also commented that ACC objected to the manner in which the SAB panel was listening to public input, and indicated that it is unclear how the Panel plans to consider those comments in its deliberations.
- Timothy Bingman, C, Du Pont de Nemours, (on the phone), urged the SAB to call on the EPA to incorporate the recommendations of the NAS before the dioxin reassessment or policies are finalized. He also urged the SAB to consider the following: 1) EPA has yet to quantitatively address the uncertainty with the TEFs; 2) EPA's position regarding the role that dietary and endogenous AhR ligands play in the toxicity of dioxin like compounds (DLCs) is unclear, and suggest that EPA discard that text suggesting that naturally occurring AhR agonists are already inducing a level of AhR activity that may be of physiological significance; and that EPA should not use this concept to support linear low dose extrapolation; 3) EPA should develop endpoint-specific TEFs; 4) EPA should consider new information as it becomes available.
- Sue Chiang, Center for Environmental Health (CEH), commented that she was concerned about production of dioxin as a result of electronic waste because of its cumulative effect. She urged EPA to meet 2010 deadline in order to protect health of the American public.
- Marcus Cooke, Cooke Companies International, commented that important literature on dioxin and cancer may have been filtered out. Specifically, he referred to the Finland study, entitled "*Soft-Tissue Sarcoma and Dioxin: A Case-Control Study*" (Tuomisto et al., 2004). This Finland population had been exposed to TCDD and dioxin-like compounds through dietary fish. The study consisted of 110 patients with soft tissue sarcoma (STS) (surgery cases) and 227 area and age-matched controls. This study found no increased risk of STS associated with increased dioxin exposure, and challenged the use of acute exposure over human epidemiology.
- Laura Olah, Citizens for Safe Water Around Badger, (on the phone) commented that the U.S. military operates munitions test and training ranges covering tens of millions of acres of land and waters in the United States. The Defense Science Board has estimated that over 15 million acres of land in the United States are potentially contaminated with unexploded ordnances. Prescribed and accidental range fires on munition sites, as well as open burning and open detonation of unserviceable munitions disperse dioxin into the air and the environment. Service members are exposed to harmful emissions which includes dioxin at army ammunition plants or reservations. Site specific risk assessments for these military activities require contaminant toxicity values. However, EPA's

- Integrated Risk Information System does not contain final assessments for a number of contaminants, including dioxin. Ms. Olah urged SAB to support the prompt release of the dioxin reassessment.
- Dr. Wallace Hayes, toxicologist, Harvard School of Public Health, mentioned that he was one of the Hercules petition signee. He commented, that based on scientific evidence, dioxin is a non-genotoxic chemical. It is a promoter which does not cause mutation of DNA. A Linear approach is not appropriate for a promoter like dioxin. It should be recognized that dioxin is a strong promoter and that there is a threshold in carcinogenicity. Unfortunately, EPA has failed to recognize nonlinearity. With limited resources, it is beneficial to focus on carcinogenicity.
  - Joy Towles Ezell, Florida League of Conservation Voters, commented that airborne dioxin gets into the food chain including fish, meat, and milk. She urged EPA to finish the dioxin reassessment and applaud the release of dioxin report.

#### Discussion of Panel Responses to EPA's Charge Questions

The Panel chair asked the lead discussants for each section to summarize the Panel members' preliminary comments and lead the discussion of the responses to the questions.

#### *Section 2- Transparency and Clarity in the Selection of Key Data Sets for Dose-Response Analysis – Dr. Paige Lawrence*

Dr. Lawrence noted that most Panel members commented the section has transparency in many aspects. Panel members had mixed opinions on whether DLCs should be included for evaluation. Panel members believed there could be more clarity in justification of the rationale for selecting dioxin vs DLC studies. During the discussion members commented that many studies did not have dose-response relationship, and that the MOA studies could be discussed with more transparency.

#### *Section 3- The Use of Toxicokinetics in the Dose-Response Modeling for Cancer and Noncancer Endpoints – Dr. Jeff Fisher*

Dr. Fisher commented the Panel agreed with EPA's model selection. The modeling was viewed as having been done well.

Panel members commented that a more quantitative uncertainty analysis is needed, possibly including the use of Monte Carlo techniques.

The Hill coefficient used in the Emond model for CYP1a2 induction was 0.6. Panel members discussed what the value of this parameter should be and suggested that a sensitivity analysis for this parameter be conducted.

#### *Section 4- Reference Dose – Dr. Mike Luster*

The lead discussant gave a brief summary of the preliminary response prepared by Dr. Elaine Faustman.

In general, there was support for the use of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies as identifying “co-critical” effects for the RfD calculation. The endpoints of changes in sperm count and TSH levels were of public health relevance and therefore of interest for determining an RfD. Collectively, there was support for these endpoints within the context of the broader dioxin literature.

A strong voice from the Panel was given for looking at the comprehensive data base of both animal and human epidemiologic studies together due to a consistent and integrative signal of toxicity across species and endpoints for TCDD. The “collective” impact of the studies should be made stronger in the document.

Dr. Armitage, the DFO, recessed the meeting at approximately 5:25 p.m.

## **October 28, 2010**

The meeting was reconvened at 8:35 a.m. The Chair asked the lead discussants on Section 5 and 6 to present their summary of comments and lead the Panel discussion.

### *Section 5 – Cancer Assessment – Dr. Helen Håkansson and Dr. Harvey Clewell*

Dr. Helen Håkansson gave a brief summary of points discussed at the Panel’s July meeting. The Panel members generally agreed on the qualitative classification that TCDD is *carcinogenic to humans*. Panel members discussed whether the mode of action (MOA) for TCDD is understood and generally agreed that more is known about the MOA for TCDD than was presented in the draft document.

The Panel agreed that Cheng et al. (2006) is an appropriate study for inclusion. Comments from the Panel members indicated that while the Steenland et al. (2001) study had better tumor data, it had no dose data. Another comment was that if the animal data and epidemiologic data were brought together, the weight of evidence for cancer would be stronger.

Dr. Kyle Steenland (one of the contributing authors of EPA’s document) clarified the selection of key epidemiologic studies and explained that there were at least 3 studies with exposure data for dose-response assessment. In all 3 studies, dose could be estimated to get response. Total cancers increased with increasing dose. It was observed that when data were fitted with a threshold model, it did not fit as well as using a model with no threshold.

Dr. Steenland explained that the study cohort was formed by exposure to TCDD. About 700 people with pentachlorophenol exposure were excluded. The Ranch Hand Study was

confounded by 2,4-D. The serum concentration of DLCs was probably higher than TCDD. One Panel member asked about the public comment that smoking also caused cancer. Dr. Steenland replied that smoking data were not available. Internal comparison was made since blue collar population generally smoke more than the general population. The study's conclusions were based on internal analysis comparing exposed workers to control workers.

One Panel member suggested that a sigmoidal model could be used to fit data for a non-linear approach. Jeff Sartout clarified that when EPA referred to a non-linear approach, cancer RfD would be derived. Non-linear approach did not mean fitting data with a non-linear model.

The Panel had no opinion on extrapolation below background. Panel members indicated that qualitative uncertainties were well described. Panel members had mixed opinions regarding exclusion of DLCs. A few panel members thought DLCs should be considered to qualitatively inform the assessment.

Becki Clark from EPA, NCEA clarified that there were separate EPA activities on dioxin:

- 1) The EPA Risk Assessment Forum was looking at the TEQ factor.
- 2) There were regulatory activities to set cleanup goals for dioxin. However, the outcome of dioxin reassessment would supercede OSWER's PRG for dioxin.

Panel members indicated that EPA did not respond adequately to the NAS recommendation to adopt both linear and nonlinear methods of risk characterization, and derived two examples of RfD development using a nonlinear approach that was characterized as an illustrative exercise only. The Panel suggested that EPA follow the NAS recommendation to present both linear and non-linear approaches, but use linear as the preferred approach for public health protection. The Panel discussed uncertainties regarding MOA. According to EPA policy, when the MOA is not completely elucidated, the linear option is preferred. Panel members also commented that alternative PODs should be presented. One Panel member commented that the non-linear approach in EPA's cancer guideline is not extrapolation below POD, but use of a Margin of Exposure approach.

#### *Section 6 – Uncertainty Analysis – Dr. Scott Ferson*

The Panel discussed the response to the Section on charge question 6. Dr Roger Cooke (a contributing author of EPA's document) provided some comments for the Panel's consideration. Dr. Cooke explained that expert elicitation is the main source of data for quantitative uncertainty analysis. Expert judgement is looked at as scientific data. A complete quantitative analysis is highly constrained.

Dr. Cooke commented that uncertainty factors stemmed from the 1950's safety factor or reliability factor, with factors of 3 multiplied together. He also commented that using an assumed distribution of an uncertainty factor is not a good idea.

Dr. Cooke commented that uncertainty analysis was meant to enhance rational consensus. If this could not be achieved, then confusion would result. Panel chair commented perhaps something feasible could be suggested in this regard.

### *Section 1 – General Charge Questions – Dr. Tim Buckley*

Panel members commented that the document was well developed, and organized.

Dr. Buckley commented that the draft *Response to Comments* document falls short on

- a. Nonlinear approach for cancer assessment
- b. Uncertainty analysis

Some literature was suggested for consideration by EPA. One Panel member commented that he would like to see more discussion on exclusion of DLCs.

The Panel recessed for lunch at noon. The chair announced that Panel writing groups would reconvene at 1:00 p.m to prepare written responses to the charge questions. The draft written responses were submitted to the DFO at approximately 5:00 pm.

### **October 29, 2010.**

The Panel reconvened at 8:35 a.m. The Chair asked each of the lead writers to present a summary of their written responses.

### Summary of the Discussion

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

### Section 1 – Dr. Buckley

- In general, EPA has been effective in developing a clear, transparent, and logical response;
- In general, EPA has objectively and clearly presented the three key NRC recommendations;
- The Panel was particularly impressed with the process that EPA used for identifying, reviewing, and evaluating the relevant literature including a public workshop;
- The Executive Summary is important to provide a concise summary;
- Issues to be addressed: Better integration across chapters and (details in charge question 2) a clear description for inclusion and exclusion of studies/data progressing through the document is needed;

- The document needs to be more clearly written;
- A glossary may be helpful to improve clarity given diversity of users;
- The large size of the document diminishes the clarity;
- EPA's response is incomplete in considering nonlinear dose response, mode of action, and uncertainty analysis;
- With respect to hazard characterization, EPA needs to consider a more balanced assessment of negative studies.

## Section 2- Dr. Lawrence

- Panel members generally noted that this section was responsive to NAS concerns about transparency and clarity.
- Panel members believed overall clarity and transparency regarding dataset selection would be further enhanced if EPA were to make this section (and the document as a whole) more concise.
- Careful and extensive editing to revise and consolidate this section and the document as a whole) were strongly recommended.
- The Section could be structured such that it is easier to follow a study from one section of the document to another.
- The majority opinion of Panel members is that the general study criteria and considerations were scientifically justified and clearly described, and were presented in a scientifically sound manner.
- The rationale for inclusion and exclusion criteria of epidemiological and animal studies should be made stronger, and dataset selection for non-cancer and cancer endpoints has room for further clarification and justification.
- The criterion that studies must contain an explicit statement of TCDD purity should be removed.
- There was discussion (with differences of opinion among Panel members ) regarding EPA's decision to exclude DLCs. The Panel agreed that information from studies with DLCs should be used in qualitative analysis and discussion of the weight of evidence for cancer and non-cancer endpoints.
- EPA should better justify the rationale for using only TCDD for quantification. Justification should include scientific and practical reasons.
- There needs to be more discussion and clarity on the exclusion of the null epidemiologic studies.
- The criterion "Confounding and other potential sources of bias" requires clarification.
- The criterion that "statistical precision, power, and study follow-up are sufficient" needs clarification.

## Section 5 – Dr. Clewell

- Panel members agreed on the classification that "TCDD is carcinogenic to humans".

- The Agency should further expand the discussion of mode of action data available to delineate linear versus nonlinear modes of action and effects in different target tissues at different life stages.
- Panel members pointed out that much is known about TCDD toxicity and mode-of-action. Nevertheless, the Panel agreed that the exact mechanism-of-action has not been fully delineated for any distinct TCDD-toxicity end-point.
- The Agency should provide a balanced discussion of the evidence for possible modes of action, including both linear and nonlinear alternatives.
- The description of the nature of a receptor mediated dose-response needs to be expanded by including more evidence regarding the nonlinearity of the receptor mediated dose-response for dioxin.
- For cancer dose response modeling, the Panel agreed with the inclusion of the Cheng et al. (2006) study, which incorporated information on gradation of exposure.
- Expanded discussion of several other studies would support the weight of evidence for carcinogenicities in less common cancers such as lymphomas and soft tissue sarcoma.
- The Panel agreed that the approach for estimating cancer risk from animal studies was scientifically justified and clearly described.
- The Panel agreed that Cheng et al. (2006) was the appropriate study for oral slope factor development, and the selection of this study was well described.
- The Panel agreed that it was appropriate to use all-cancer mortality in Cheng et al. (2006), because of the extensive dose-response information.
- The Panel agreed that the use of the Emond model to estimate risk specific doses from the Cheng et al. (2006) study was scientifically justified and clearly described.
- Panel members agreed that DLC studies should be considered in the weight of evidence discussion.
- Panel members believed the draft dioxin document did not respond adequately to the NAS recommendation to adopt both linear and nonlinear methods of risk characterization.
- EPA should present both linear and nonlinear risk assessment approaches. EPA can still conclude that EPA policy dictates that, in the absence of a definitive nonlinear mode of action, the linear option should be preferred in order to assure protection of the public.

### Section 3- Dr. Fisher

- The Panel believed the use of whole blood concentration is a better choice than body burden for the dose-response assessment of TCDD, because it is more closely related to the biologically relevant dose metric: the free concentration of dioxin in the target tissues.
- The Panel believed the Emond model provided the best available basis for the dose metric calculations in the assessment. The scientific justification for using

- the Emond et al. model should address how the model is intended to be used in the assessment, which would then dictate why a particular model was selected.
- The Panel found EPA modifications to the model were minor and appropriate.
  - The Panel recommended additional efforts to fully characterize the uncertainty in the models with special considerations of the Hill coefficient value.
  - The Panel found the mouse model performs reasonably well. However, the Panel recommended an external peer review of the mouse PBPK model that was developed from an existing rat model.
  - The Panel believed EPA has provided an adequate characterization of the qualitative uncertainty in the mouse and rat kinetic models, sufficient to justify their use, together with the human model, to estimate rodent-to-human extrapolation factors.
  - However, a more quantitative uncertainty analysis is needed, using Monte Carlo techniques to estimate the propagation of uncertainty from the PBPK model parameters to the dose metric predictions.
  - The modeling of the Cheng et al. (2006), Mocarelli et al. (2008), and Baccarelli et al. (2008) studies needed to be described in more detail and the impact of the model parameter uncertainty and exposure uncertainty in these studies should be evaluated quantitatively.
  - The draft dioxin document only presented the sensitivity analysis published by Emond et al. (2006), which was not entirely adequate for the purposes of this assessment. The analysis left out the Hill coefficient, which was one of the most important parameters in the model for low-dose extrapolation. A sensitivity analysis of the model should be provided to authenticate the model for its intended purpose.
  - The Panel agreed with the average daily dose calculation approaches described in the draft dioxin document. However, calculation of the early life stage internal doses should be carefully explained.

#### Section 4- Dr. Luster

- The Panel agreed with the use of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies for identifying “co-critical” effects for the RfD calculation. The Panel believed that, overall, EPA provided a well thought out and rational discussion of why these two human studies were selected for determining the RfD.
- The Panel believed a more balanced discussion of these two studies should be provided by providing a better description of the potential weakness in the studies.
- The Panel noted that similar Point of Departure (PODs) were found across a broad spectrum of other reported dioxin toxicities in multiple species. The Panel believed the strength of the RfD should not be based solely on these two human epidemiology studies, but rather should be supported by integration with other similar supporting dioxin and DLC studies.

- The Panel indicated that the pattern of exposure from Seveso posed some extrapolation issues for the EPA. Issues raised included the question whether the same endpoints and or dose response would be expected from such exposure scenarios with high acute exposures when extrapolating to low-dose chronic exposure. The Panel noted that it would be useful for EPA to provide a discussion of published examples in which dioxin studies were conducted using both high-dose acute and low-dose chronic exposures in animals for the same endpoint and how the outcomes compare both qualitatively and quantitatively.
- There was general support for EPA's approach of using the WHO reference value for determining TSH levels and there were strong suggestions that further discussion of WHO reference values for male reproductive parameters should be included.
- The Panel generally supported EPA's decision to use the Baccarelli et al. (2008) estimates of the relevant effective doses.
- The Panel agreed with EPA that the appropriate uncertainty factors (UFs) were included but suggested that EPA provided justification for not including an UF for data quality for the two Seveso studies.

The Panel recessed for lunch at noon and reconvened at 1:00 pm.

#### Section 6- Dr. Ferson

- The Panel found Section 6 to be clearly presented, but not scientifically justified.
- Although EPA's decision not to do an integrated quantitative analysis might have been justified on grounds of practicality, overkill, or timeliness, the Panel believed that quantitative uncertainty analysis is an integral part of good assessment.
- The Panel recommended that EPA consider omitting altogether or strongly revising Section 6, particularly its argument that quantitative uncertainty analysis is unfeasible for the dioxin assessment.
- The Panel believed that a quantitative uncertainty analysis is possible, though EPA may decline to do one on other grounds.
- The Panel did not recommend Monte Carlo analysis that was mentioned during discussion of Charge Question 3 because it requires many assumptions that cannot be justified by appeal to data.
- The Panel commented there are several ways one could do quantitative uncertainty analysis, without expert elicitation. These include:
  - Probability trees or model choice tree;
  - Sensitivity studies, even if not completely comprehensive;
  - Nesting of intervals;
  - Probability bounds analysis including Bayesian p-boxes which has been used in a variety of applications, including assessments at two Superfund sites;
  - Info-gap decision theory which has been used in several applications; and
  - Robust optimization.

- Bounding analysis is an uncertainty analysis technique. At a minimum, EPA could propagate simple bounds. Selecting precise probability distributions may be hard, but ranges are easier.
- Value of information approaches could be used to clarify whether modeling uncertainties and disagreement significantly affect risk estimates.
- Validation, e.g. via a “reality check” against the total number of cancers predicted versus observed in a population, could be discussed in the chapter.
- Epistemic uncertainty (page 6-5) is not what the document says it is. Epistemic uncertainty reflects imperfect knowledge, such as from limited data or imperfect causal understanding about a system. It does not imply that a quantity about which there is epistemic uncertainty is necessarily fixed.
- The word “exotic” (used to describe some methods discussed in Section 6) should be excised from the document. More generally, the tone of Section 6 seems condescending and should be strongly edited to be more neutral.
- The Panel recommended that EPA purge the document of the notion of “volitional uncertainty”. EPA should display the different modeling choices and the consequences of making them.
- The Panel recommended keeping and expanding the sensitivity analyses.

The Panel chair summarized 3 scientific issues to be included in the Letter to the Administrator:

- Uncertainty analysis - it is important to have some uncertainty analyses incorporated.
- Cancer dose-response – non-linear methodology and mode of action analysis need to receive more attention.
- DLCs were excluded in the assessment. The Panel recommended DLCs be considered qualitatively in the dioxin assessment, although the Panel was not asking EPA to change the inclusion criteria.

The Panel recognized how important it is for EPA to finish this document in a timely manner. However, the scientific issues should be addressed.

### Next Steps

Dr. Buckley thanked the Panel for their active participation. He asked the lead writers to provide revised response to charge questions to the DFO in 3 weeks.

Ms. Clark and Dr. Vu thanked the Panel, and the meeting was adjourned at approximately 2:15 p.m.

Respectfully Submitted:

Certified as Accurate:

/signed/

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Diana Wong, Ph.D., DABT  
Designated Federal Officer

/signed/

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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**

#### **CHAIR**

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