

**Summary Minutes of the
U.S. Environmental Protection Agency (EPA)
Science Advisory Board (SAB)
Trichloroethylene (TCE) Review Panel
Public Meeting of May 10 - 12, 2010**

Date and Time: Monday, May 10, 2010: 9:00 AM – 5:00 PM
Tuesday, May 11, 2010: 9:00 AM – 5:30 PM
Wednesday, May 12, 2010: 8:30 AM – 2:00 PM

Location: Hilton Washington Embassy Row Hotel
2015 Massachusetts Ave NW, Washington, DC 20036

Purpose: To review EPA's Toxicological Review of Trichloroethylene draft document.

Attendees:

Committee members present: All members attended. See panel roster¹

SAB staff office: Dr. Ghazi Dannan, Dr. Marc Rigas, Dr. Holly Stallworth, Dr. Vanessa Vu

EPA Office of Research and Development (ORD) Staff:

Dr. Stan Barone*, Mr. David Bussard, Dr. Jane Caldwell*, Dr. Weihsueh Chiu, Dr. Glinda Cooper, Dr. Marina Evans*, Dr. John Fox, Dr. Kathryn Guyton, Dr. Maureen Gwinn, Ms. Karen Hammerstrom, Dr. Jennifer Jinot, Dr. Abdel Kadry, Dr. Nagalakshi Keshava*, Dr. Susan Makris, Dr. Brian Pachkowski, Dr. Peter Preuss, Ms. Cheryl Siegel Scott, Dr. Bob Sonawane, Mr. Paul White

Other EPA Staff: Ms. Shari Bauman, Office of Water

Federal Employees: Dr. Nancy Beck, Office of Management and Budget; Ms. Katherine Kurtz*, U.S. Navy; Dr. Resha M. Putzrath, U.S. Navy

Members of the public:

Ms. Pat Casano, General Electric Corporation; Dr. Wolfgang Dekant*, University of Wurtzberg; Dr. John DeSesso, Exponent; Dr. Michael Dourson*, Toxicological Excellence for Risk Assessment; Dr. Paul Dugard, Halogenated Solvents Industry Alliance; Mr. Jerome Ensminger*, TFTPTF.com; Ms. Maria Hegsted, Inside EPA; Dr. Michael Kelsh*, Exponent; Mr. Caffey Norman, Patton Boggs, LLC; Mr. Michael Partain*, TFTPTF.com; Dr. Lorenz Rhomberg, Gradient Corporation; Ms. Pat Rizzuto, BNA; Dr. Lisa Sweeney*, Toxicological Excellence for Risk Assessment; Mr. Steve Via, American Water Works Association;

*Attendance via telephone

Meeting Materials:

All materials discussed at the meeting are available on the [SAB Web site](#), at the [May 10-12 TCE Review Panel Meeting](#) page.

Summary of Discussion:

The meeting was announced in the Federal Register² and proceeded according to the meeting agenda³. Dr. Marc Rigas, the Designated Federal Officer (DFO), convened the meeting at 9:00 AM on May 10, 2010. He stated that as required under the Federal Advisory Committee Act (FACA), the Committee's deliberations are held in public with advance notice given in the Federal Register, and the meeting minutes will be made publicly available after the meeting. He stated that the TCE Review Panel received 9 written public comments in advance of the meeting and 11 requests for oral public comment. He also stated that Committee Members are subject to federal ethics regulations and conflict-of-interest laws that pertain to them. He then turned over the meeting to Dr. Vanessa Vu, SAB Staff Office Director for a few introductory remarks and then to Dr. Deborah Cory-Slechta, Chair of the TCE Review Panel. Dr. Cory-Slechta initiated a roll call of panel members.

The following is a summary of the issues discussed and conclusions reached during the meeting.

A. Acknowledgement from Dr. Peter Preuss, Director of EPA's National Center for Environmental Assessment within the Office of Research and Development (ORD)

Dr. Preuss presented a brief history of the Toxicological Review of Trichloroethylene and some of the key features and science issues⁴

B. Public comments

The panel heard public comments from 11 speakers. A list of speakers is available⁵. Some speakers used slides, and these are available⁶

C. Meta-analysis of cancer epidemiology (Charge Question 2)

Lead discussants were generally in agreement with EPA's presentation of the meta-analysis which carefully considered comments in the report from the National Academy of Sciences (NAS) in 2006. The criteria for including studies in the meta-analysis are clear, and the discussion of confounding is strong. Panel members raised questions about the inclusion of lymphomas, given limited epidemiologic evidence and also about other possible cancer site meta-analyses, such as sites identified by some of the individuals during public comment. Panel members indicated that EPA was conservative in the selection of cancer sites, only including three for which there is the strongest evidence. Panel members also indicated that prior meta-analyses available to the NAS in 2006 were not found to be as strong.

D. PBPK Modeling (Charge Question 1)

Panel members discussed the EPA's PBPK model used for prediction of internal dose metrics and interspecies extrapolation. Reviewers believed that the new applications of PBPK modeling in lieu of default assumptions are to be commended and that the hierarchical Bayesian approach, (i.e., using mouse posterior distributions as prior distribution for rat and rat posterior as a prior for human) makes sense. It was agreed that this represents a substantial step in PBPK modeling from that developed in the EPA Trichloroethylene Health Risk Assessment released in 2001. In addition, the panel encouraged the use of PBPK methods as an alternative to default assumptions in risk assessment.

Reviewers did express concerns about the transparency and clarity of the model description, as it is a very complex model. There are a number of parameters being fitted in this model, for which there may be little data. For some parameters, the prior and posterior distributions are very similar, and the reasons for this were not clearly stated.

The committee then discussed the logistics of running the model with EPA staff. Staff commented on the long time it takes for each model run. Reviewers stated that EPA should be explicit in indicating that they are limited by computational power from carrying out model runs for inter-individual variability in humans.

E. Hazard Assessment: Cancer (Charge Question 4)

The committee discussed EPA's classification of TCE as carcinogenic by all routes of exposure. Charge question discussants found the meta-analysis to be clearly described and appropriate, and to provide a compelling case for the carcinogenicity classification according to the EPA 2005 cancer guidelines. Several Panel members added that the argument is further supported by the consistency of the animal toxicology data to the epidemiology studies. Several questions were raised about the specifics of EPA's cancer guidelines and addressed by EPA SAB staff and program office staff. The SAB staff agreed to provide copies of relevant sections of the Cancer Guidelines to panel members at the evening break on the first day.

A few Panel members raised questions about the meta-analysis, which they found reliant on few studies. These members also believed that the individual epidemiology studies, themselves were not strong enough. The Panel decided to resume the discussion the next day, after Panel members received and reviewed copies of EPA's Cancer Guidelines.

F. Hazard Assessment: Role of Metabolism (Charge Question 5)

Panel members concurred that EPA presented a reasonably complete picture of extant research on TCE metabolism, but that better integration and synthesis of the information was required as well as a critical and quantitative comparison of studies to clarify controversial aspects of TCE metabolism, toxicity and bioavailability. Many studies use corn oil gavage, which may have an impact on bioavailability. Overall, the Panel agreed with EPA that TCA alone does not account for all liver effects.

May 11, 2010

Dr. Keil and Dr. Rankin, who were unable to attend the previous day, joined the Panel and were introduced. EPA staff were then granted time to make further comments on the PBPK modeling and the Bayesian analysis. In a subsequent discussion of Bayesian analysis, several Panel members indicated that EPA's methods are reasonable, but require better explanation in the document, including additional clarity about issues of variability and uncertainty.

G. Hazard-assessment: non-cancer (Charge Question 3)

Panel members found the discussion of non-cancer animal data to be thorough in the document. Panel members found that the document appropriately recognizes study limitations. The section could, however, be better integrated and redundancies eliminated. It was pointed out that a human multi-center study in France may be worth including in this section and references will be provided.

With regard to health endpoints, members found the discussion of immune effects to be sound, including the discussion of autoimmune processes, which are particularly compelling. The liver toxicity data was believed to be well covered, and there is an enormous body of research in this area, a well understood aspect of TCE carcinogenicity. The neurotoxicology section is strong, relying mostly on older well-established data sets.

Panel members commented that it would be worth adding the potential for a relationship between immune suppression and cancer, as a possible cancer mode of action at the less frequently reported sites (e.g. breast, lung, etc.).

H. Hazard assessment: mode(s) of action (Charge Question 6)

Panel members generally agreed that the document clearly described the relevant scientific studies. A concern was raised regarding the focus on single MOAs for each endpoint, as it seems combination of MOAs will probably account for interspecies differences. Panel members agreed with EPA that there is inadequate data to conclude that TCE-induced cancer and non-cancer effects in rodents are not relevant to humans.

Panel members indicated the need to be clear about support for the interpretation of a mutagenic mode of action for cancer, as this affects the response to Charge Question #10 regarding age-dependent adjustment factors. A mutagenic mode of action was deemed reasonable by the Panel, but it was also stated that the data on the Von Hippel-Lindau (VHL) mutations for kidney cancer are currently too uncertain to draw any conclusions. Members commented that it might be prudent to substitute the idea of uncertainty for complexity in describing the mode of action for kidney tumors.

The issue of liver tumors and PPAR α agonism was discussed briefly with EPA Staff. The panel agreed that PPAR α agonism may not be the only event involved and liver enlargement also needs to be considered. One member indicated that using the term uncertainty dampens the body of evidence, which is pretty clear.

I. Susceptible populations (Charge Question 7)

Panel members agreed that the document thoroughly covers the literature regarding population variability and provides good qualitative information about differences in exposure and metabolism. However, additional discussion of how this translates into differences in risks and health effects needs to be incorporated, including data limitations and associated research needs. Some Panel members expressed concern with the assertion by EPA that variability in healthy human adults can be captured by the EPA PBPK model, particularly as the data used to generate the model was from a limited number of human subjects.

J. Return to address question on Hazard assessment: cancer (Charge Question 4)

The Panel resumed discussion of cancer hazard assessment after reviewing the EPA 2005 Cancer Guidelines. Members stated that though the effect is modest, the epidemiology is strong and that the evidence is consistent with classification as carcinogenic to humans. While it was indicated that the document could be more objective with respect to null results, the Panel agreed that the kidney cancer evidence alone supports the classification and with the causality criterion stated in the cancer guidelines (e.g., Hill criteria, exposure-response, multiple studies).

K. Dose-response: methods and results for non-cancer (Charge Question 8)

For this detailed and specific charge question related to quantitative assessment, panel members generally expressed agreement with conclusions of the document, but found that each step is dependent upon calculations in previous steps, making it difficult to quantitatively validate. One member commented that toxic nephrosis should not be included because the data is based on a LOAEL at a high dose, so its inclusion for low dose risk assessment is not meaningful. Reviewers expressed support for the benchmark dose analysis. Several reviewers expressed concerns about the kidney metabolism data used to derive the RfC and RfD for that endpoint, consistent with issues raised by the public commentators. These issues may be valid, though the panel members found them to be less of a concern as endpoints besides the kidney endpoint support the same conclusions in regard to effect levels.

L. Dose-response: Methods and results for cancer (Charge Question 9)

Panel members raised questions about basing the entire cancer risk assessment solely on the Charbotel study. Members suggested analyses that included control for cutting oil exposure, since these oils are also carcinogenic. The possibility of a non-linear low dose response was discussed, with some members commenting that some low exposure epidemiology studies did not discern a cancer effect.

M. Age-dependent Adjustment factors (Charge Question 10)

Discussion of the age-dependent adjustment factors was brief. The panel members supported the application of age-dependent adjustment factors and found them to be clearly and transparently described.

After discussion of these ten charge questions, Dr. Cory-Slechta asked that any additional research needs and suggestions for the last two charge questions be sent to her by email to compile for Panel

review in the report. She then made assignments of lead writers for each charge question. She explained the lead writer's role in consolidating information from relevant panel members and crafting a consolidated response for discussion with the panel on May 12.

Lead writers for each charge question were assigned from the subgroups as follows:

Charge Question	Lead writer
1	Dr. Emond
2	Dr. Vena
3	Dr. Dietert
4.	Dr. Vena
5	Dr. Rusyn
6	Dr. Weaver
7	Dr. De Roos
8	Dr. Post
9	Dr. Pennell
10	Dr. Portier

May 12, 2010

The panel reconvened and each lead writer briefly presented a draft consolidated opinion for their charge question. The slides on the draft responses presented by the subgroup at the meeting are available on the SAB Web site⁷.

A panel member commented during subsequent discussion that no specific mention had been made of hazards related to male reproductive effects. Dr. Cory-Slechta subsequently indicated that this was an oversight, and that two panel members, Dr. Ornella Selmin and Dr. Deborah Keil would provide specific comments related to these sections. Dr. Keil and Dr. Selmin stated they had no concerns with EPA's work in this area, which represents a minor component of the Agency's assessment.

Due to time constraints and need for additional discussion on several charge questions, Dr. Cory-Slechta proposed that an additional teleconference be scheduled in late June. In preparation for the call, lead writers for each charge question will work further to develop a draft consensus response. Following this call, the draft committee report will be developed and discussed in a conference call to be scheduled for August. The Panel agreed to this plan.

Dr. Rigas adjourned the meeting at 2:00 PM on May 12, 2010.

Respectfully Submitted:

Certified as True:

/SIGNED/
Dr. Marc Rigas
Designated Federal Officer

/SIGNED/
Dr. Deborah Cory-Slechta, Chair
Trichloroethylene (TCE) Review Panel

ATTACHMENT A: Roster

U.S. Environmental Protection Agency Science Advisory Board Trichloroethylene (TCE) Review Panel

CHAIR

Dr. Deborah Cory-Slechta, Professor, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY

MEMBERS

Dr. Scott Bartell, Assistant Professor, Program in Public Health, University of California - Irvine, Irvine, CA

Dr. Aaron Blair, Scientist Emeritus, National Cancer Institute, National Institutes of Health, Rockville, MD

Dr. Anneclaire De Roos, Associate Professor, Department of Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA

Dr. Rodney Dietert, Professor, Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, NY

Dr. Claude Emond, Adjunct Clinical Professor, Department of Environmental and Occupational Health, Faculty of Medicine, University of Montreal, Montréal, QC, Canada

Dr. Montserrat Fuentes, Professor, Department of Statistics, North Carolina State University, Raleigh, NC

Dr. David G. Hoel, Distinguished University Professor, Department of Biometry and Epidemiology, Medical University of South Carolina, Charleston, SC

Dr. Gunnar Johanson, Professor, Department of Toxicology and Risk Assessment, Karolinska Institute, Solna, Sweden

Dr. Deborah Keil, Associate Professor, Clinical Laboratory Sciences, University of Nevada, Las Vegas, Las Vegas, NV

Dr. Jose Manautou, Associate Professor & Marlene L. Cohen and Jerome H. Fleisch Scholar, Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, CT

Dr. David McMillan, Associate Professor, Cell and Molecular Pharmacology, Nebraska Medical Center , University of Nebraska Medical Center, Omaha, NE

Dr. Michael Pennell, Assistant Professor, Division of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH

Dr. Kenneth M. Portier, Director of Statistics, Department of Statistics and Evaluation, American Cancer Society, National Home Office, Atlanta, GA

Dr. Gloria Post, Research Scientist, Office of Science, New Jersey Department of Environmental Protection, Trenton, NJ

Dr. Gary Rankin, Professor and Chair of Pharmacology, Physiology and Toxicology, Pharmacology, Physiology and Toxicology, Joan C. Edwards School of medicine, Marshall University, Huntington, WV

Dr. Ivan Rusyn, Associate Professor, Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Dr. Ornella Selmin, Associate Research Scientist, Nutritional Sciences, Shantz Building 38, Room 309, University of Arizona, Tucson, AZ

Dr. Brian Thrall, Technical Group Leader , Cell Biology Group , Pacific Northwest National Laboratories, Richland, WA

Dr. John Vena, Professor and Department Head, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA

Dr. Virginia Weaver, Associate Professor, Departments of Environmental Health Sciences & Medicine, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

SCIENCE ADVISORY BOARD STAFF

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Materials Cited

The following meeting materials are available on the SAB Web site, <http://www.epa.gov/sab>, at the [May 10-12, 2010 TCE Review Panel Meeting](#) page:

¹ TCE Review Panel Roster, May 10 – 12, 2010 (Attachment A)

² Federal Register: March 31, 2010 (Volume 75, Number 61, pp. 16108-16109).

³ Final Agenda for May 10-12 TCE Review Panel meeting

⁴ Dr. Peter Preuss Presentation slides (Agency briefing material)

⁵ See “Individuals requesting to address the Panel during public comment period” (SAB Staff Office material)

⁶ See “Slides from presentations made to panel during public comment period in order presented” (Public Comment submitted to the SAB Staff Office)

⁷ See “See subgroup presentations on draft charge response” (Committee members’ comments)