

**Summary Minutes**  
**U.S. Environmental Protection Agency**  
**Science Advisory Board**  
**Chemical Assessment Advisory Committee Augmented for the Trimethylbenzene Review**

**Date and Time:** Wednesday November 5, 2014 1:00 PM – 5:00 PM  
Friday November 7, 2014 1:00 PM – 5:00 PM

**Location:** Meeting conducted by teleconference

**Purpose:** Review and discuss the Science Advisory Board Panel’s October 9, 2014 draft review of the IRIS Toxicological Review of Trimethylbenzenes and Recommendations to improve IRIS assessments.

**Attendees:**

Chemical Assessment Advisory Committee Augmented for the Trimethylbenzene Review (TMB Panel)<sup>1</sup>

Members:

Dr. Cynthia Harris, Chair	Dr. Lawrence Lash
Dr. James V. Bruckner	Dr. Frederick J. Miller
Dr. Mitchell Cohen	Dr. Lorenz Rhomberg
Dr. Deborah Cory-Slechta	Dr. Stephen M. Roberts
Dr. Gary Ginsberg	Dr. Emanuela Taioli
Dr. Helen Goeden	Dr. Raymond York
Dr. Sean Hays	
Dr. Robert A. Howd	

SAB Staff Office: Mr. Thomas Carpenter, Designated Federal Officer

Others Present: Please see Members of the Public Attending Meeting: Attachment A

**Meeting Materials:** All meeting materials are available on the SAB website at the Chemical Assessment Advisory Committee (CAAC) Augmented for the Review of the EPA’s Draft IRIS Trimethylbenzenes Assessment webpage:  
<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/13D0528B52050E1F85257D38007701FB?OpenDocument>

**Convene Meeting**

The meeting was announced in the Federal Register<sup>2</sup> and proceeded according to the meeting agenda, as revised. Mr. Thomas Carpenter, Designated Federal Officer (DFO) for the Chemical Assessment Advisory Committee (CAAC) Augmented for the Review of the EPA’s Draft IRIS Trimethylbenzenes Assessment, convened the meeting at 1:00 p.m. on November 5, 2014 and noted that this teleconference would be continued on November 7, 2014 beginning at 1:00 p.m.. He stated that the EPA Science Advisory Board (SAB) is a chartered federal advisory committee and reviewed Federal Advisory Committee Act (FACA) requirements. He stated the Panel members are in compliance with federal ethics requirements that apply to them and noted that the SAB Staff Office has determined that there are no issues with conflict of interest or appearance of a loss of impartiality for any of the Panel members.

As the DFO, Mr. Carpenter stated he would be present during the panel's business and deliberations. He stated that summary minutes of the meeting would be prepared by the DFO and certified as accurate by the Chair. Mr. Carpenter also noted the EPA staff from the Office of Pesticide Programs and National Center for Environmental Assessment would be on the line if panel members had questions.

### **Introduction of Members, Purpose of Meeting, and Review of the Agenda**

Dr. Cynthia Harris, Chair of the TMB Review Panel, hereafter referred to as the panel, provided introductory remarks.

Dr. Harris welcomed the panel and members of the public in attendance. She stated that the meeting was convened to review and discuss the Science Advisory Board Panel's October 9, 2014 draft review of the IRIS Toxicological Review of Trimethylbenzenes (August 2013) and EPA's progress in addressing the NRC recommendations to improve the development of IRIS assessments.

Dr. Harris reviewed the meeting agenda<sup>3</sup> and provided an overview of how the panel would conduct their deliberations for the teleconference. She also acknowledged that there were three requests from the public to provide oral comments for the Panel's consideration. After the oral public comments, the panel members would discuss the sections of the draft panel report, noting substantive edits and identifying key recommendations for the letter to the Administrator and executive summary. She also urged members to identify recommendations that need to be made for the TMB assessment to be completed as distinct from other suggestions that would improve the TMB assessment. Dr. Harris asked panel members if they had any clarifying questions. Hearing none, she proceeded to the agenda and introduced the agency staff for their presentations.

### **Clarifying Remarks from EPA's National Center for Environmental Assessment**

Dr. Vincent Cogliano, Interim Director of EPA's IRIS program, thanked the panel for their work in developing the draft report. He asked that the panel consider clarifying several sections of the report:

- Please identify recommendations that must be addressed in the TMB assessment and those recommendations that are in response to the NRC recommendations and may be addressed in IRIS assessments in general
- There seems to be some ambiguity in the recommendations for using the physiologically based pharmacokinetic (PBPK) model of Hissink and the Jarnberg and Johansson models. Does the agency need to conduct a comparison of the two models?
- There is also some ambiguity on conducting BMD modeling and the PBPK in suggested modifications to the approach on pages 23 and 29.

### **Public comments**

Three individuals registered to address the panel. The presentations received by the SAB Staff Office are posted on the SAB website. The presenters were:

Ms. Patricia K Casano, General Electric, noted that General Electric is a member of the Aerospace Industry Association. She did not provide specific comments on the IRIS TMB Toxicological Review or the draft SAB TMB report. She wanted to make the panel aware of the current need to find an alternative solvent for trichloroethylene, one alternative is trimethylbenzenes. She asked the panel to consider their discussion on uncertainty and the quantitative impact that may have on

alternative solvents and carefully consider EPA's guidance on uncertainty factors in developing their recommendations.

M. David Adenuga, Ph.D., ExxonMobil Biomedical Sciences, Inc addressed the panel and his oral statement<sup>4</sup> is posted on the SAB website. Dr. Adenuga noted that the panel addressed issues he presented at the June meeting in the draft report's discussions on C9 aromatic mixtures and oral toxicity study on 1,3,5-TMB. He noted the EPA's Office of Pesticide Programs recently published an exemption tolerance for the C9 aromatic hydrocarbons<sup>5</sup> and provided a summary of the action to the panel. Panel members noted that they have included recommendations on mixtures in the report. One panel member noted that data on mixtures are not interchangeable with data and information on individual TMBs as suggested by Dr. Adenuga.

Nancy B. Beck, Ph.D., American Chemistry Council provided an oral statement that is also posted on the SAB website.<sup>6</sup> She noted that many of the recommendations in the report are supported by ACC. ACC comments are focused on areas of improvement to the report. She stressed that consensus is important and the panel should strive to reach consensus. She also noted that the recent Office of Pesticide Programs C9 rich aromatic exemption for tolerances was provided to the panel. She also encouraged the panel to develop recommendations that do more than suggest re-evaluation of determinations in the assessment. She stated that the panel needs to recommend an action and not suggest, as EPA will not necessarily fully re-evaluate an issue that is suggested. She also noted that the reliance on reversible endpoints may not be appropriate. She expressed concern that developing subchronic values is addressed by other agencies and the IRIS program has been focusing on chronic values. She noted the preamble recommendations are important and encouraged the panel to make clearer recommendations on the IRIS enhancements including systematic review. Lastly she asked for clarification on the panel's recommendation that the PBPK model, when modified, should receive an external independent review.

### **Discussion of the Responses to Charge Questions**

The Chair and members discussed that recommendations in the draft report need to provide clear, direct answers to the charge questions. They noted that comments from the EPA and the public requested that they provide clarity in specific sections. Members agreed that as they move through the sections of the report on the teleconference they would clarify the importance of recommendations, identify advice that needs to be addressed in finalizing the TMB assessment and differentiate when advice can be incorporated into future IRIS assessments.

Members noted that the discussion on the C9 fraction is in multiple sections of the report and should be discussed in a single section of the TMB report and refer the reader to that section of the SAB report.

### TMB Assessment Executive Summary

Members had minor comments on the recommendations for the TMB assessment Executive Summary

### Literature Review

Members discussed the recommendation to develop a database or tool for listing the papers and studies considered in the assessment. Some members noted that a link and search function such as that used in Medline would be helpful. Other members noted that such a recommendation could significantly delay the TMB assessment and other IRIS assessments. They cautioned that unanticipated impacts could result from this recommendation. Another member suggested that

an appendix listing the papers and articles and documenting the decision for inclusion or exclusion using a standard vocabulary defining the criteria may suffice. Members noted that the goal of this recommendation is to transparently provide the agency's decision on the papers and studies considered, excluded and selected for IRIS assessments. Lead authors will revise this section for the next draft.

#### Hazard Identification and Mixtures

One member noted that the role of the C9 mixture studies in this toxicological review is touched upon in a number of places with seemingly inconsistent views expressed. While the report acknowledges that there are differences of opinion among the panel on this topic, expressing different views in different sections of the report is not the best way to handle this. Members discussed the Hazard Identification section and agreed this is the most logical place to address C9 mixture studies.

Some members noted that the TMB assessment is being developed to address exposure to TMB isomers detected at Superfund sites and not exposure to mixtures. They noted that the use of mixture data increases uncertainty and may not be appropriate for the individual TMB isomers. Other members noted that the C9 fraction cannot be dismissed. They suggested that a rationale should be developed for the use or exclusion of these data and to correct the inconsistencies in the current draft report.

Members discussed the use of mixture data to fill data gaps and whether these data should be further considered on the basis that they represent the toxicology of a relevant mixture. They acknowledged that this may be limited given that the content of any single TMB isomer is less than 50%, that the combination of TMBs represent less than 60% of the mixture and that the nature of interaction between individual TMB isomers and other components in the mixture has not been studied. Lead authors will add language to the report that EPA should take a cautious approach in using these studies to fill TMB isomer data gaps and in the main body of the toxicological review should provide a clearer assessment of the extent to which the mixtures studies add to the overall hazard evaluation of each isomer.

#### Physiologically Based Pharmacokinetic Modeling

Members discussed the draft language on the use of the PBPK modeling and identified errors and sections that lack clarity. Members agreed on how the PBPK model was used and where the panel has concerns that needs to be highlighted. The PBPK model was used for:

- Species extrapolation for derivation of the RfCs for 1,2,3,-TMB and 1,2,4-TMB.
- Dose-route extrapolation to derive the RfDs for 1,2,3-TMB and 1,2,4-TMB (extrapolating from the RfCs).

Members also discussed the recalibration of the Hissink model and using the Jarnberg and Johansson model. Members concluded that restarting the assessment with the Jarnberg and Johansson model for a comparative analysis with modified Hissink Model is not needed. Members discussed whether the recommendation should be: (1) adjust the Hissink model by recalibrating metabolic pathways, hepatic blood flow, or other methods to improve the model's fit, or (2) use benchmark dose (BMD) modeling of the Korsak and Rydzynski (1999) data using air TMB concentration as the dose metric to derive the point of departure and subsequently use the PBPK model to convert the point of departure to the weekly average blood TMB

concentration. Members noted the BMD approach is a simpler and better approach that is scientifically appropriate and will most likely be less resource intensive.

Members discussed the dose metric approach and uncertainties that may arise from the limited knowledge about the mode of action and use of the weekly average venous blood. They agreed that given the recommendation for the BMD approach this approach for an internal dose metric is reasonable.

#### RfC for 1,2,4-TMB and 1,2,3-TMB

Members discussed the report's presentation of statistical analysis of the "reversibility of effects." Some members found the language unclear and other members found that statistical analysis in the TMB assessment could be interpreted to support a reversibility of effects. Members agreed to add more detail to the statistical comparison among rotarod failure and controls to support the panel's finding that effects are not reversible. Members did not identify additional data or information that would require changes to the section on the RfC for 1,2,3-TMB.

#### RfC for 1,3,5-TMB

Members noted that the draft report is not clear on how the agency should use the Saillenfait et al. (2005) study and whether the extrapolation from 1,2,4-TMB is the panel's preferred approach. Members noted that the limitations of Saillenfait et al. are (1) the short exposure period and (2) the study does not have a neurotoxicity endpoint for comparison to Korsak and Rydzynski. Members agreed that the agency's use of Saillenfait et al. needs to be corrected and used as a candidate RfC. The members also agreed that the RfC for 1,3,5-TMB based on the neurotoxicity from the Korsak and Rydzynski study and extrapolation from 1,2,4-TMB is appropriate and valid. The recommendation should be to correct the Saillenfait candidate RfC and use neurotoxicity as the critical effect.

#### RfD for the TMB isomers

Members discussed the RfD sections for the three isomers. Members noted that the extrapolation for the RfD for 1,2,4-TMB and 1,2,3-TMB are appropriate. They noted that the Koch Industries (1995) study needs to be considered by EPA. They noted one of the limitations of the Koch Industries study is there is no neurotoxicity endpoint. Members also noted that the Adenuga et al. (2014) is a recent manuscript of the 1995 study conducted by Koch Industries and not an original study.

Members agreed that the agency's approach to extrapolate from the inhalation to the oral route is appropriate and the same approach should be used for all three isomers. The draft report should introduce the oral data for 1,3,5-TMB in the discussion of the RfD for 1,2,4-TMB and as appropriate refer to that section of the report. The 1,3,5-TMB oral study should be considered consistent with the IRIS program's development of candidate toxicity values for evaluation.

#### **Adjourn**

At 4:55 p.m. the Designated Federal Officer adjourned the meeting for the day and noted the panel would reconvene on Friday, November 7, 2014 at 1:00 p.m. (ET), to continue through the agenda.

### **Reconvene the meeting**

The Designated Federal Officer reconvened the teleconference on Friday, November 7, 2014 at 1:00 p.m. (ET)

#### Uncertainty Factors

Members noted that the discussion on mixtures, reversibility and the toxicological equivalence of the TMB isomers may raise some issues that may need to be clarified in the uncertainty discussion of the report. One member asked if the toxicological equivalence across the congeners raises an issue that they could be treated as cumulative exposure. Other member disagreed and stated that the isomers should not be treated additively. Another member noted that the Superfund program could add the isomers together in developing hazard indexes. A different member noted that the dose curves may change if an additive approach is used. Members agreed to add this discussion under the UF<sub>D</sub> and UF<sub>S</sub> section of the report and noted that there was not consensus across the panel on this issue.

#### Susceptible Life Stages

Members discussed the need for this section to be consistent with the Hazard Identification section of the report and the discussion of appropriate data to fill gaps in the literature. Members agreed that it is important for the agency to address susceptible life stages in assessments and identified some minor editorial changes.

#### Subchronic RfCs and RfDs

Members discussed the general need for subchronic toxicity values and noted that EPA and public commenters expressed concern about the recommendation to include subchronic values in the assessment. Some members expressed concern that there is no IRIS guidance or method for developing short duration exposure toxicity values. Others members noted that there is a need for these types of values and the panel suggested editorial changes to acknowledge subchronic values may not always be appropriate, however the panel found that the recommendation should stay in the report.

#### Responding to the NRC Recommendations

Members noted that they generally agree with the draft report sections addressing the NRC recommendations (Sections 3.1.1, 3.1.2, 3.1.3). However several members noted the responses are long and it is difficult for readers to separate the specific recommendations from the text. Members agreed that the authors would revise this section, adding headers and bullets restating the recommendations from the text.

#### Addressing Public Comments on the May 2012 draft

Members noted that issues in this response to the charge question are addressed in the review of the current draft report (i.e., C9, mixtures and oral toxicity data on 1,3,5-TMB). Members agreed that adding references to those sections of the draft report discussion was appropriate.

### **Opportunity for brief clarifying remarks**

There were no requests from the agency or the public to provide clarifying remarks.

### **Action Items and Next Steps**

Writing teams will redraft sections of the report and submit them to the DFO. The DFO and Dr. Harris will redraft the letter to the Administrator and the Executive Summary of the report to be consistent with the new sections and the panel's discussion. The DFO will schedule another teleconference to discuss the next draft of the report.

The Designated Federal Officer adjourned the meeting at 4:00 p.m.

Respectfully Submitted:

Certified as Accurate:

*/Signed/*

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Mr. Thomas Carpenter  
SAB Designated Federal Officer

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Dr. Cynthia Harris  
Chair

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the Panel members. The reader is cautioned not to rely on the minutes represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations

### **Materials Cited**

All meeting materials for the November 5 and 7, 2014, teleconferences of the Chemical Assessment Advisory Committee Augmented for the Trimethylbenzene Review are available on the SAB website <http://www.epa.gov/sab>. The materials cited below for this meeting are available at the following address:

<http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/13d0528b52050e1f85257d38007701fb!OpenDocument&Date=2014-11-05>

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- 1 Roster SAB Chemical Assessment Advisory Committee Augmented for the TMB Review
  - 2 Federal Register Notice Announcing the Meeting (79 *FR* 62436 - 62437)
  - 3 Meeting Agenda
  - 4 Hydrocarbon Solvents Panel/American Chemistry Council Oral Comments to EPA/SAB Teleconference on SAB Draft Report on EPA IRIS Assessment of Trimethylbenzene (November 5, 2014)
  - 5 C9, C10–11, and C11–12 Rich Aromatic Hydrocarbons; Exemption from the Requirement of a Tolerance (Federal Register 79 57805-57810)
  - 6 Oral Statement from The ACC Dr. Nancy Beck

**Attachment A**  
**Members of the Public Who Requested Call-in Information for the**  
**CAAC TMB Review Panel Teleconference**  
**November 5 and 7, 2014**

**Attendees <sup>1</sup>**

Dr. David Adenuga, ExxonMobil Chemical Company  
Dr. Nancy Beck, American Chemistry Council  
Mr. Jon Busch, ACC  
Ms. Patricia Rizzuto, Bloomberg BNA  
Ms. Patricia Casano, General Electric  
Dr. Lyle Burgoon, US Environmental Protection Agency  
Ms. Angela Curry, Texas Commission on Environmental Quality  
Dr. Lynn Flowers, US EPA  
Ms. Maria Hegstad, Inside Washington  
Dr. Samantha Jones, US EPA  
Ms. Gina Perovich, US EPA  
Mr. Lawrence Reichle, US EPA  
Ms. Christine Ross, US EPA  
Dr. David Brussard, US EPA  
Mr. Andrew Kraft, US EPA  
Dr. Resha Putzrath, Navy and Marine Corps Public Health Center  
Mr. Robert Fensterhiem, RegNet Environmental Services  
Ms. Halie Choi, RegNet Environmental Services  
Ms. Audrey Galizia USEPA  
Bridget O'Brien USEPA  
Mr. Kerry Liefer, US EPA  
Mr. John Vandenberg, USEPA  
Dr. Paul Schlosser, USEPA  
Mr. Joe DeSantis, USEPA  
Ms. Susan Rieth, USEPA  
Ms. Mary Ross, USEPA  
Ms. Connie Meacham, US EPA  
Ms. Kathleen Newhouse, USEPA

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<sup>1</sup> Based on members of the public requesting the teleconference dial in information