

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

Date and Time: Tuesday June 17, 2014 9:00 AM - 5:00 PM
Wednesday June 18, 2014, 8:30 AM - 5:30 PM
Thursday July 19, 2014 8:30 AM – 5:00 PM

Location: Meeting conducted via face to face meeting and teleconference

Purpose: To receive briefings on the IRIS Program, the development of the EPA’s IRIS *Draft Toxicological Review of Trimethylbenzenes* (August 2013), and to develop responses to the EPA charge questions.

Attendees:

Chemical Assessment Advisory Committee Augmented for the Trimethylbenzene Review TMB Panel¹

Members:

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

SAB Staff Office: Mr. Thomas Carpenter, Designated Federal Officer
Mr. Christopher Zarba, Director, Science Advisory Board Staff Office

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

Meeting Materials: All meeting materials are available on the SAB Web site at the Chemical Assessment Advisory Committee Augmented for the Review of the EPA’s Draft IRIS Trimethylbenzene Assessment page.

<http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/c30edc1934b7e8ba85257c97004c9cac!OpenDocument&Date=2014-06-17>

Convene Meeting

The meeting was announced in the Federal Register² and proceeded according to the meeting agenda, as revised. Mr. Thomas Carpenter, Designated Federal Officer (DFO) for the Chemical Assessment Advisory Committee Augmented for the TMB Review (hereafter the TMB Review Panel), convened the meeting at 9:00 a.m. on July 17, 2014. He stated that the EPA Science Advisory Board (SAB) was a chartered federal advisory committee and reviewed Federal

Advisory Committee Act (FACA) requirements. He stated that 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; those determinations are summarized on the SAB website.³

He stated that for this review, the SAB Staff Office had convened an augmented panel inviting member of the Chemical Assessment Advisory Committee and additional experts to participate in the review of the *IRIS Toxicological Review of Trimethylbenzenes (August 2013)*. This panel will develop responses to the Charge for this peer review. The Charge was two-fold and requested: (1) a review of the scientific and technical analyses used to develop reference concentrations and reference doses for the three trimethylbenzene isomers; and (2) advice and comment on the enhancements to the IRIS Program implemented to address the NRC recommendations.

Mr. Carpenter stated that as DFO, he would be present during the panel's business and deliberations. He stated that summary minutes of the meeting would be prepared and certified as accurate by the Chair.

Welcoming Remarks

Mr. Christopher Zarba, SAB Staff Office Director, welcomed the panel members and thanked them for providing advice to EPA on this IRIS assessment.⁴

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

Dr. Cynthia Harris, Chair of the TMB Review Panel, provided introductory remarks.

Dr. Harris welcomed the panel and members of the public participating in the meeting. She stated that the meeting was convened to respond to the charge provided to the SAB and to consider the data and information that would support approaches to develop inhalation reference concentrations (RfC) and oral reference doses (RfD) for the three trimethylbenzene isomers (1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB). The agency also evaluated the carcinogenic information available and has asked the panel whether the information was sufficient to develop a quantitative assessment for TMBs. After a brief introduction of panel members, Dr. Harris reviewed the meeting agenda⁵ and provided an overview of how the panel would conduct their deliberations to provide advice in response to the charge questions. She noted that after the panel discussions, they would develop a report for distribution among panel members for further discussion with the goal of reaching consensus on the recommendations and advice.

Dr. Harris noted that EPA would provide introductory remarks to the panel and would be available throughout the meeting for clarifying questions as they arose. She also acknowledged the one member of the public that requested to provide oral comments for the panel's consideration. After the public comment, the lead discussants and the panel members would deliberate on responses to the Charge questions and discuss their comments. Dr. Harris invited members of the public to register to provide comments on the issues raised during the panel's discussions on response to the charge questions for a brief public comment period at the end of the first day. Dr. Harris asked panel members if they had any clarifying questions. Hearing none she proceeded to the agenda and introduced the agency staff for presentations.

Remarks from EPA's National Center for Environmental Assessment on enhancements to the IRIS program

The morning session provided members with an update of the IRIS program's progress in addressing the National Research Council recommendations for improving the development of IRIS assessments in general. Four agency leaders gave presentations and responded to clarifying questions from panel members.

Dr. Kenneth Olden, Director of EPA's National Center for Environmental Assessment (NCEA), provided an overview of the IRIS program, its importance to the agency and the agency's approach to the Draft Toxicological Review of Trimethylbenzenes as one of the first IRIS assessments to address the NRC recommendations for improving the development of IRIS assessments. Dr. Olden noted the increase in stakeholder and expert participation in the IRIS process in addition to the SAB reviews. He also thanked the panel members and the SAB for their efforts.

Dr. Vincent Cogliano, Interim Director of the IRIS program, provided a more detailed presentation of the enhancements the agency has made to the IRIS process. He noted that the agency is implementing the enhancements in a phased approach and the TMB assessment was well under development when the NRC recommendation were published and the agency incorporated as many of the recommendations as possible to still publish this assessment. His presentation is on the SAB webpage.⁶

Dr. Samantha Jones, Associate Director for Science for the IRIS program, presented the agency progress in adopting the principles of systematic review to help ensure standardized approaches across IRIS assessments and to ensure that major science decisions are rigorously vetted.⁷

Ms. Gina Perovich, Acting Deputy Director for the IRIS program, presented upcoming activities in the program. Her presentation identified public workshops and meetings. She also spoke about the new document structure and IRIS template compared to the old structure. Lastly she identified assessments that are under development and the current stage of each assessment.⁸

Remarks from EPA's National Center for Environmental Assessment on the Draft Trimethylbenzenes Toxicological Review

Mr. J. Allen Davis, TMB Assessment Manager, presented an overview of the TMB Assessment. Mr. Davis' presentation⁹ is posted on the SAB website. He discussed the key aspects of the Toxicological Review, especially how toxicological similarities between TMB isomers and toxicokinetic modeling were used to fill in data gaps in isomer-specific databases and provided some clarification on science issues that were raised by public commenters at the teleconference held on May 22, 2014.

Members asked clarifying questions about whether EPA considered deriving a mixture assessment and the need to have RfCs and RfDs for individual isomers due to detection at Superfund sites. Another member noted that it is difficult to attribute the toxicokinetic effects in mixtures as they may be antagonistic or protagonistic compared to the individual TMB isomers.

Public comments

One individual registered to address the panel and two others provided written comments. The oral presentation given by Dr. David Adenuga, ExxonMobil Biomedical Sciences, Inc.¹⁰ is

posted on the SAB website. Additional written comments provided by two individuals are posted on the SAB website for this meeting.¹¹ The commenters were:

Dr. Nancy Beck, American Chemistry Council

Mr. Jonathan T. Busch Hydrocarbon Solvents Panel, American Chemistry Council

Dr. Adenuga's presentation¹² described the role and composition of the ACC Hydrocarbon Solvents Panel and discussed additional information on the C9 aromatic fraction and inhalation studies. He also discussed the use of pain sensitivity as the critical endpoint, uncertainty factors, availability of oral data for TMBs, and provided the Hydrocarbon Solvent Panel's recommendations for the TMB assessment. Dr Adenuga also introduced a recent publication for oral toxicity of 1,3,5-TMB.¹³ Members asked clarifying questions about the inhalation data, the comparability of vehicle emission studies presented by Dr. Adenuga, and how the C9 mixture may alter adsorption, distribution and metabolism for the individual isomers.

Discussion of EPA's Charge questions

Panel members discussed the Charge questions and asked the EPA staff clarifying questions on the charge questions. Members noted that there are overlapping issues between the charge questions for the TMB isomers and that the life stage issues still need to be addressed. Members also noted that the Charge questions were discussed in a May 22, 2014 teleconference and did not have further questions for the agency.

Members noted that there were no specific charge questions regarding sensitive life stages for the derivation of the RfCs and RfDs.

Discussion of Responses to Charge Questions

Hazard Identification-Synthesis of Evidence (Question 1)

Drs. Howd, Lash, and Rhomberg were the lead discussants for this section. Lead discussants noted the effort the agency has made in presenting this section. They identified several areas where the synthesis of evidence section could be improved:

- An introduction on the scope and goal of the synthesis section
- Use of the mixture data (i.e., C9 fraction)
- Use of other alkylated aromatics that could fill data gaps for the TMB data, and
- Limitations of the TMB database need to be clearer.

Members noted that the TMB assessment was to address exposure to individual TMBs at Superfund sites and that the individual TMB data were used rather than data for TMB mixtures. Members discussed the potential uses of data on mixtures and similar compounds, including how they might be used to identify modes of action, further support the uncertainty factor selection and fill other data gaps in the TMB dataset. Several members noted that mixture data are not directly comparable to the individual TMB data as there may be competing and inhibitory interaction among the components in the mixtures. One member noted that the differences in chemical and physical properties (i.e., Henry's Law constant) may explain the differences.

Members discussed the potential uses of the C9 fraction data. Some members noted that the data could be used for a comparative analysis, it may be useful to the assessment qualitatively to

inform the discussion on available TMB data. Other members found the differences in the TMB data and the C9 data limited its usefulness. One member suggested that an appropriate synthesis of the evidence – at a minimum – needs to identify that data on the C9 fraction and similar alkylated aromatics are available and why the agency is or is not using these data.

Hazard Identification-Summary and Evaluation (Questions 1 and 2)

Drs. Goeden, Howd, Lash, and Rhomberg were the lead discussants for the non-cancer discussion in this section. They noted that while there is a lack of data for the 1,2,3-TMB and 1,3,5-TMB isomers for the chosen critical effect, neurotoxicity, the selection was biologically plausible and reasonable. Panel members noted that the endpoints among the studies are very different. Another member noted the limited chronic data and the need to extrapolate from subchronic data and questioned whether exposures in the subchronic studies had arrived at a steady state. Several members noted that the mode of action is not known for the neurotoxicological endpoint. The extrapolation from subchronic to chronic exposure and the lack of mechanism adds to the uncertainty.

Members also discussed the approach used to compare studies noting that the agency has not yet developed a systematic review. Other members noted that a discussion of data gaps should be identified in this section and discussion further clarified about how those gaps influenced uncertainty factors used to develop the RfC and RfDs.

Member discussed how the agency compared different studies and noted that the assessment needs a more clear discussion of the agency's process.

Drs. Beland and Taoli were the lead discussants for the carcinogenic discussion in this section. The panel agreed with the agency that there is inadequate information on the carcinogenic potential for TMBs. Members of the panel provided additional citations and studies.

One member noted that there was no discussion of sensitive lifestages in the assessment other than in the preamble and suggested that there should be a discussion that states why the agency has not addressed sensitive life stages in this assessment. The panel agreed to add a section in the report to address the lack of information and provide alternative approaches using similar compounds and a qualitative descriptions of potential effects.

RECESS FOR THE DAY

At 5:00 p.m., Mr. Carpenter, DFO adjourned the panel in recess until 8:30 a.m. Wednesday, July 18, 2014.

RECONVENE

Mr. Carpenter reconvened the CAAC TMB Panel at 8:30 a.m. and the panel resumed discussion of responses to the Charge questions.

Toxicokinetics and Pharmacokinetic Modeling (Question 1 and 2)

Drs. Bruckner, Hays, and Krishnan led the discussion on the selected physiologically based pharmacokinetic (PBPK) model. Lead discussants had some initial concerns on the use of the Hissink rat PBPK model rather than the Jarnberg and Johansson human PBPK. They noted that human partition values are higher in the rat model and this may lead to over-prediction. EPA noted that the agency requested the Jarnberg and Johansson model from the authors but it was not provided.

One member noted that a quality review of the Hissink model and EPA's approach to dropping the high dose accounts for any over-prediction in the Hissink model and that the Jarnberg and Johansson model would require additional modification. Another member noted that the Hissink model was re-parameterized. A member also noted that the lung gas exchange portal assumes 100 percent bioavailability and this may also be creating the over-prediction at higher doses.

Members noted that there are differences in the methods and parameterization between the two models as well as the isomers.

One member provided a detailed review of the model¹⁴ and noted specific parameters that could be re-evaluated by the agency but noted that the approach is reasonable. Members suggested including the review as an appendix to the draft report.

Drs. Cohen, Goeden, Howd, and Miller led the discussion on the dose metric selection. They noted that the agency's use of venous blood concentrations is reasonable and adequately discussed. They discussed the presentation of the 1,2,4-TMB data and whether a steady state was achieved. Members noted that data on arterial blood concentration to the brain are not available and the selected dose metric seems adequately characterized, however the assessment should clarify the agency's approach to using venous blood level and how the average was computed. They noted that the over-prediction to the dose response might create an overly conservative analysis.

Other members agreed that the agency approach is reasonable. They noted that the EPA needs to better account for the two-fold under-prediction of blood data and the three-fold difference for the dose response range difference.

Inhalation Reference Concentration (RfC) for 1,2,4-TMB (Question 1, 2, 3, and 4)

Drs. Cory-Slechta, Cohen, Howd, and Miller were the lead discussants for the selection of the critical study (Korsak and Rydzyński 1996) and selection of the endpoint of decreased pain sensitivity for 1,2,4-TMB. The lead discussants agreed with the selection of Korsak and Rydzyński and provided recommendations to clarify the agency's summary of the study and its selection. The hotplate test and its outcome, time to pawlicking after administration of an aversive stimulus, is a scientifically valid outcome measure for derivation of the RfC. This test, and variants thereof, has been widely used to evaluate nociception pathways, mechanisms and potential interventions and their relation to nervous system function. These tests are more typically used to evaluate acute pain, but in some variants delayed pain or neuropathic pain can be evaluated.

Several members asked about the irreversibility of the effect. Another member noted that toluene has a different reaction than TMB in the "pawlick test" and may be relevant to the C9 mixture and TMB discussion. Another member noted that the extrapolation from subchronic to chronic will need further discussion in the uncertainty factors discussion. One member was not convinced that the effect persists and suggested to recast the section to discuss irreversibility and any other effects that may occur at lower doses.

Panel members agreed that Korask and Rydzyński study is an appropriate selection. The recommendations for this question should have EPA: refine the terminology to be consistent in the assessment, consider data from shorter exposures, compare results to other solvents and clarify the statistical analysis used in the studies.

Drs. Bruckner, Hays, Ginsberg, and Krishnan were the lead discussants for the benchmark dose, human equivalent dose used in the PBPK model to identify the point of departure for the RfC for 1,2,4-TMB. The benchmark dose (BMD) modeling approach appears to have been appropriately conducted and adequately described and referenced. The duration-adjusted point of departure (POD) was converted to a POD_{HEC} by use of the PBPK model of Hissink et al. (2007). Members noted that EPA dropped the high dose from the Korsak and Rydyski study to improve the model fit to the data and suggested several possible analyses to evaluate differences between the modeled RfC and the developed RfC. The analyses are: comparing the bench mark dose developed using external air concentrations; using the Hissink model to derive internal dose in the rat at the point of departure; and using the human PBPK model to calculate human equivalent concentrations associated with internal dose in rats at the point of departure. One member noted that the use of 1 standard deviation is a default in the EPA guidance and there is no additional justification that explains the strengths or weakness of the data. Other members noted that the guidance is well established and reasonable. Members agreed that dropping the high dose group is a reasonable approach and recommended a better explanation of the defaults and options the agency used.

Drs. Howd, Lash, Miller, and Roberts were the lead discussants for the uncertainty factors discussion for 1,2,4-TMB. Discussants noted that the agency has guidance, *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002), for developing uncertainty factors. The panel discussed five areas of variability and uncertainty that were considered by the EPA in deriving the proposed RfC for 1,2,4-TMB. They noted that the assessment defines each uncertainty factor (UF) and the major considerations that are used to select each particular value. UF values are listed in Table 2-4 on page 2-14 for the 5 target organs and potential critical effects within each organ system. The members identified five uncertainty factors and discussed each separately. The uncertainty factors are:

- UF_A – an interspecies uncertainty factor;
- UF_H – an intraspecies uncertainty factor;
- UF_L – a LOAEL (lowest observed adverse effect level) to NOAEL (no observed adverse effect level) uncertainty factor;
- UF_S – a subchronic to chronic uncertainty factor; and
- UF_D – a database uncertainty factor.

UF_A – Members generally agreed with the UF_A of 3 and the agency's rationale. In developing the RfC for 1,2,4-TMB, the EPA used PBPK modeling to convert estimated internal doses in rats in toxicity studies of 1,2,4-TMB to corresponding applied doses in humans. Use of the PBPK modeling reduced uncertainty associated with extrapolating animal exposures to humans based upon toxicokinetic differences. Uncertainty regarding possible toxicodynamic differences among species (i.e., different sensitivity to toxicity at equivalent internal doses) remains, justifying keeping the other half-log component of 3.

UF_H . The panel agreed with the UF_H of 10 and its rationale, although one member suggested that a UF_H of 3 would be more appropriate based on human susceptibility to general anesthetics, which only varies by a factor of about 2. On this basis a UF_H of 3 could be selected given the neurotoxicity endpoint used to establish the POD. Other TMB panel members disagreed, stating that the mode of action of neurotoxicity of 1,2,4-TMB is unknown and that the actions of general anesthetics may have little or no bearing on variability in TMB susceptibility.

UF_L. Members agreed with EPA choices for UF_L values. However, they noted that the justification for the UF_L could be strengthened. In conducting BMD modeling, a BMR equal to one standard deviation change in the control mean for modeled endpoints was selected. Explanation of the reasoning for selection of one standard deviation (versus one-half standard deviation) should be added to the document along with a clearer discussion of why this is expected to lead to a POD for which a UF_L of 1 is appropriate.

UF_S. Member discussed the using a UF_S of 3 and 10. One member thought that a UF_S of 10 would be more appropriate. When the data used to generate a chronic RfC are from subchronic studies, a UF_S is used to address uncertainty whether longer exposures might lead to effects at lower doses. They note that this uncertainty factor accounts for reversibility of neurotoxic, hematological, and respiratory effects. Most of the panel were in agreement with the agency selection. Others believed that the reversibility of effects should be accounted for in the UF_S.

UF_D. Most of the panel agreed with the UF_D of 3, but several members thought that the UF_D should be 10. Those panel members who agreed with a UF_D of 3, found the justification provided by the EPA to be satisfactory, while others thought that toxicity data available for C9 mixtures should contribute to the rationale to lower the value from the default of 10. Others disagreed with including C9 mixture data as relevant to the database UF. Members who thought that the UF_D should be 10 cited the absence of data in other species, the absence of a multi-generational reproductive study, and the absence of a developmental neurotoxicity study alone warranted a full factor of 10. An additional point made by one panel member was that because the RfCs for all of the isomers are being set at the same value, whereas the database is severely limited for the 1,2,3-TMB and 1,3,5-TMB isomers, that the latter two compounds deserve a UF_D of 10 and should be used for all isomers.

Inhalation Reference Concentration (RfC) for 1,2,3-TMB (Questions 1, 2, 3, and 4)

Panel members noted that the four charge questions for 1,2,3-TMB are identical to the questions they discussed for the inhalation RfC for 1,2,4-TMB. They noted that the agency used the 1,2,4-TMB information and data to develop the RfC and the agency should address the same advice and recommendations provided for 1,2,4-TMB. Members noted that there are not chemical-specific data for the 1,2,3-TMB isomer and the report could refer the reader to the previous discussion of 1,2,4-TMB.

Inhalation Reference Concentration (RfC) for 1,3,5-TMB

Drs. Cory-Slechta, Cohen, Goeden, and York were the lead discussants for the RfC for 1,3,5-TMB. Discussants noted that they are not aware of a subchronic inhalation study for this isomer and there is one isomer-specific inhalation-based developmental toxicity study (Saillenfait et al. 2005). While this study was considered as a potential study to define a critical effect for the 1,3,5-TMB RfC derivation, members identified several issues in how the agency developed an RfC. They also noted the endpoint is developmental toxicity and not neurotoxicity.

Members noted that the extrapolation from 1,2,4-TMB is scientifically supported as the isomer profiles are similar. Members discussed how the 1,3,5-TMB RfC could be developed using the Saillenfait data by correcting maternal and developmental LOAELs in the study. The panel also

noted that the agency should discuss the selection of Korsak and Rydzynski (1996) as the appropriate study once the developmental RfC is recalculated.

Oral Reference Dose (RfD) for 1,2,4-TMB (Questions 1, 2, and 3)

Drs. Bruckner, Ginsberg, Hays, Krishnan, and York were the lead discussants for the response to Charge questions on the oral and route-to-route exposure data used to derive the RfD for 1,2,4-TMB. Discussants noted that there are no oral studies for 1,2,4-TMB. Members agreed that the modified Hissink et al. (2007) is a reasonable starting point and the oral dose route is simplistic and therefore it is acceptable for the current purposes; i.e., the dose metric used for dose response modeling (parent compound average weekly venous concentration) is not sensitive to peaks and valleys of a more normal oral intake pattern. Members did note that the Koch study for 1,3,5-TMB was not used by the agency and that it should be considered and discussed.

Drs. Howd, Lash, Miller, and Roberts were the lead discussants for the response to Charge questions on the uncertainty factors used to derive the RfD for 1,2,4-TMB. They generally agreed with the UFs selected in the development of the oral RfD for 1,2,4-TMB. They noted that the discussion of uncertainty could be strengthened with respect to bioavailability assumptions. They noted a logic in the EPA using the same UFs for the oral RfD as were used in the development of the inhalation RfC. Members discussed whether additional uncertainty is associated with the oral intake component in the PBPK model, specifically with regard to assumptions made with that component regarding oral absorption of 1,2,4-TMB and first-pass metabolism.

Oral Reference Dose (RfD) for 1,2,3-TMB (Questions 1 and 2)

Panel members noted that the charge questions for 1,2,3-TMB raise the same issues and considerations as the questions they discussed for the inhalation RfD for 1,2,4-TMB. They noted that the agency used the 1,2,4-TMB information and data to develop the RfD and the agency should address the same advice and recommendations provided for 1,2,4-TMB. Members noted that there are not chemical-specific data for the 1,2,3-TMB isomer and the report could refer the reader to the previous discussion of 1,2,4-TMB.

RECESS FOR THE DAY

At 5:30 p.m., Mr. Carpenter, DFO, adjourned the panel in recess until 8:00 a.m. Thursday, July 19, 2014.

RECONVENE

Mr. Carpenter reconvened the CAAC TMB panel at 8:00 a.m.

Oral Reference Dose (RfD) for 1,3,5-TMB (Questions 1 and 2)

Drs. Bruckner, Ginsberg, Hays, and Krishnan were the lead discussants for the response to Charge questions on the data and route-to-route exposure used to derive the RfD for 1,3,5-TMB. Members noted that the agency rejects an oral study by Koch Industries (1995). The Koch Industries study was the only isomer-specific and route-specific study available in the peer-reviewed literature for oral exposure to 1,3,5-TMB when the TMB Assessment was drafted. A recently published paper by Adenuga et al. (2014) is also available. Members did not agree that the Koch study should have been rejected from the data set for this assessment. Members agreed

that, at a minimum, these studies should be used to develop a candidate RfC for consideration. They noted that the Koch Industries study is not a neurotoxicity study and may have limitations and differences from the EPA's approach that should be discussed in the assessment. Members noted that the POD from the Koch Industries study could also be used in the RfD derivation. Other members thought the study could be used qualitatively in the assessment. Some members thought the agency should consider using the Koch Industries study for the RfD for the other isomers. Other members thought that the analysis and comparison needs to be conducted first.

Drs. Howd, Lash, Miller, and Roberts were the lead discussants for the response on whether the RfD for 1,3,5-TMB is clearly presented and scientifically supported. They thought the presentation of the extrapolation from 1,2,4-TMB was clear but the document needs to address the selection over the Koch Industries study. They noted the discussion on the previous charge question identified issues the agency should address and members agreed that these modifications are needed.

Carcinogenicity of 1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB

Drs. Beland and Taioli were the lead discussants for the charge questions on the carcinogenicity of the TMB isomers. Members agreed with the agency's assessment of the evidence for carcinogenicity of trimethylbenzenes. They noted that the data set is limited and was well presented by the EPA in the draft toxicological review. Members provided additional references for the agency to include.

Literature Search Strategy/ Study Selection and Evaluation

Drs. Beland, Howd, Krishnan, and Taioli were the lead discussants for this section of the Charge. Members agreed that the search strategy, databases, and search terms were clearly articulated. They noted that the flow chart provided (Figure LS-1) to tabulate the studies that were included and excluded was helpful. Members, however, found that the description of the study selection is not transparent and the agency should further clarify the criteria for omitting studies. While it was clear which papers were used in the draft assessment, there was no means of determining which papers were excluded from the assessment. Thus the review does not provide sufficient documentation to determine if important papers may have been overlooked or considered and then omitted from consideration based on EPA's criteria.

Members noted that 65 papers were excluded "based upon manual review of paper/abstracts" and there was no means of determining the identity of these papers. They noted certain papers were excluded because they were "not available in English" and found this criterion for omission to be unacceptable. The selection process also excluded papers because they were "in vitro studies" yet in vitro studies are mentioned in the assessment (e.g., Janik-Spiechowicz et al., 1998; page 1-46); thus, it was not clear if only certain in vitro studies were included and what factors were used to determine if these studies should be excluded.

One member noted that the description of the search strategy did not mention related alkylated aromatic compounds. Because of the similarity to TMBs this may have resulted in important papers being excluded. Other members asked whether this expansion of the search is warranted or would add too many papers of limited relevance. Members discussed including a summary table of the studies related to each health effect: for example, a table with the nine studies on neurotoxicity in humans, reporting study design, inclusion, exclusion criteria, number of

subjects, and main results. This is common practice in epidemiologic reviews and meta-analyses. Members noted that the current way of presenting the study selection has some advantages because it is very analytical, but it is also hard to summarize.

Executive Summary

Drs. Beland, Cohen, and Taioli were the lead discussants for the review of the Executive Summary. They note that the Executive Summary condenses the large amount of information presented in the draft TMB Assessment and the Supplemental Information. Members noted there is always tension to find the appropriate level of detail to include in the Executive Summary. Members also noted that the draft TMB Assessment presents somewhat detailed information on the data used to develop the RfC and RfD for each of the three isomers and that detail may detract from the intended purpose of brevity. Members agreed the summary should be truncated to emphasize the major conclusions. Specifically, citations should be removed from the summary unless they are absolutely essential. For example, members noted that there are whole sections discussing confidence, the agency should consider discussing this in one section.

General Charge Questions (Questions 1, 2, 3, and 4)

Drs. Beland, Cory-Slechta, Howd, Rhomberg, and Roberts were the lead discussants on the General Charge questions and how the IRIS program is responding to the NRC recommendations. They also led the discussion of the summary of public comments presented in Appendix F.

Members discussed the enhancements to the preamble and noted there have been many improvements. One member suggested making the preamble into a separate document while others disagreed and thought the agency should tailor preambles to the specific compounds under review. Others noted the TMB preamble was not very helpful in setting the stage for the PBPK modeling used in this assessment. Other members pointed to the preambles in International Agency Research on Cancer (IARC) as an example. A member also noted that the IRIS preamble is not a guidance document and the agency should be careful not to paraphrase guidance to the extent that the preamble is seen as guidance.

Members discussed the National Academy of Science recommendations and that there may be an evolving nature in developing the preamble. EPA staff noted that these assessments are the early release of the preamble and the agency is trying to develop a “road map” to the assessments. Other member noted that the Preamble is too long.

Members discussed how the process and the key outcomes are presented in the assessment. They noted that there are multiple objectives and needs in presenting the correct level of detail for the assessments readers. They noted that a consistent presentation of studies (i.e., standardized tables) would be helpful. This consistent presentation in tables and organization is important within each document and would be good to have across assessments. They noted that while the document focuses on choices made in the analysis (e.g., selection of endpoints) it is also important to provide interpretations and justification of why those choices were made.

Members discussed how the document could better describe the literature and made similar points to the previous discussion. Members noted that choices in the literature search may be too exclusive. One member noted that the literature search is only a step to developing a systematic

review that the IRIS program is working toward. Members found the dose response comparison and tabulation of points of departure (PODs), health effects concentrations (HECs), and applied uncertainty factors (UFs) helpful. They noted that both the Hazard Identification and Dose-Response sections jump to the first endpoint or analysis to be considered, and then have separate sections on each and suggested an overview to prepare a reader for what is coming or to identify what is critical versus those that are there for completeness.

Members discussed how well the assessment considers the critical studies. They found, in general, that a great deal of progress has been made in restructuring IRIS assessments to focus on interpretations, choices, and analyses, and relegating the supporting information to appendices. Members thought the process of systematic review still needs development. Documenting the literature search has progressed, but further development is needed in establishing standard practices for abstracting relevant data, for evaluating study quality, strengths and shortcomings, and for integration of evidence across studies.

Members discussed whether the EPA adequately addressed the scientific issues raised in the public comments on the May 2012 draft of the assessment. In general, members thought that summary of public comments on Appendix F of the TMB Assessment addressed issues raised in public comments and that explanations were furnished for the agency's stance on the issues and their disposition. One member noted that the agency addressed the issues summarized according to the agency's judgments, and those judgments were transparently discussed.

The panel was divided, however, on the adequacy of some of the responses and the advisability of the dispositions that were made as presented in the summary. In particular, there was a variety of views on the role that testing of the C9 fraction should have in the assessment, with some panelists accepting the reasons for omission of this from the main evaluation and others feeling that these results had a role that had not been adequately explored. There was also disagreement among the panelists related to the interpretation of the pain sensitivity data, with some members questioning whether the document adequately examined the question of reversibility following termination of exposure. Members agreed that the SAB report needs to address the C9 fraction and reversibility.

Public Comment on the Panel's Deliberations

Dr. David Adenuga registered to address the panel and provide oral comment and clarification on the panel's discussion. He thanked the panel for their consideration and reiterated his view that the panel should recommend that the agency use the C9 fraction data and the oral toxicity data for 1,3,5-TMB in his recent study.

Discussion of Remaining Issues and Next Steps

Dr. Harris and panel members reviewed the points and key issues developed by the panel¹⁵ and asked the panel for any additional thoughts. Panel members agreed that the key issues were identified and did not identify any additional issues or comments. Dr. Harris asked the DFO to summarize the next step for panel members to develop the Advisory Report

Mr. Carpenter stated that writing teams would work to develop draft sections of the Advisory Report and submit them to the DFO. The DFO and the Chair would develop the draft Advisory report with the draft Letter to the Administrator and draft Executive Summary based on key issues from the panel's discussion and draft text. The panel would then reconvene to review the

draft Advisory Report by teleconference in approximately 6 weeks. Based on the discussion a second draft Advisory report would be distributed for consensus review. After consensus, the draft Advisory report would be submitted to the chartered Science Advisory Board for Quality Review prior to finalization. Mr. Carpenter agreed to develop a writing schedule and request available times for the teleconference from panel members.

Dr. Harris asked the panel for any questions or clarifications. She then called upon the DFO to adjourn the meeting.

The Designated Federal Officer adjourned the meeting at 5:15 p.m.

Respectfully Submitted:

Certified as Accurate:

/Signed/

/Signed/

Mr. Thomas Carpenter
SAB Designated Federal Officer

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 SAB Chemical Assessment Advisory Committee Augmented for the TMB Review are available on the SAB Web site: <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/MeetingCal/C30EDC1934B7E8BA85257C97004C9CAC?OpenDocument>

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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 16324-16325)
 - 3 [Determination Memorandum and Biosketches of Candidates](#)
 - 4 Draft *Toxicological Review of Trimethylbenzenes* In Support of Summary Information on the Integrated Risk Information System (IRIS) (CASRN 25551-13-7, 95-63-6, 526-73-8, and 108-67-8)
 - 5 Meeting Agenda
 - 6 Presentation by Dr. Vincent Cogliano, Interim Director IRIS Programs US EPA
 - 7 Presentation by Dr. Samantha Jones, Associate Director of Science IRIS programs US EPA
 - 8 Presentation by Ms. Gina Perovich, Acting Deputy Director, IRIS US EPA
 - 9 Overview of the Draft IRIS Assessment of Trimethylbenzenes. Mr. J. Allen Davis, IRIS USEPA

- 10 Comments on Behalf of ACC's Hydrocarbon Solvents Panel Comments to CAAC Regarding EPA's Draft Assessment of TMBs. Dr. David Adenuga, 6/17/ 2014
- 11 Public Comments from the American Chemistry Council and ACC Hydrocarbon Solvents Panel received by the DFO
- 12 Comments on Behalf of ACC's Hydrocarbon Solvents Panel to CAAC Regarding EPA's Draft Assessment of TMBs. Dr. David Adenuga June 17, 2014
- 13 Adenuga et al. 2014 The sub-chronic oral toxicity of 1,3,5-trimethylbenzene in Sprague-Dewey rats. Regulatory Toxicology and Pharmacology
- 14 Review of Timethylenenes PBPK Model Internal Metrics. Dr. Sean Hays, June 2014.
- 15 Compilation of Slides and Discussion Points the TMB Panel Discussed in Developing Responses to the Charge Questions. June 19, 2014.

Attachment A
Members of the Public Who Requested Call-in Information for the
CAAC TMB Review Panel Teleconference
June 17-19, 2014

Attendees

Dr. David Adenuga, ExxonMobil Chemical Company
Dr. Nancy Beck, American Chemistry Council
Mr. Jon Busch, ACC
Mr. Kevin Bromberg, Small Business Administration
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
Ms. Linda M. Wilson, Attorney General Office State of New York
Dr. Angela Nugent, US EPA
Mr. Thomas Brennan, US EPA
Dr. Ken Olden, US EPA
Mr. James Rollin, Policy Navigation Group
Dr. Patrick Beatty, American Petroleum Institute
Dr. David Brussard, US EPA
Ms. Kacee Deener, US EPA
Mr. Andrew Kraft, US EPA
Mr. Eric Somerville, US EPA

Attendees (via Phone)¹

Dr. Laura Keller, ExxonMobil Chemical Company
Dr. Richard McKee, ExxonMobil Chemical Company
Dr. Resha Putzrath, Navy and Marine Corps Public Health Center
Dr. Chuck Elkins
Mr. Robert Fensterhiem, RegNet Environmental Services
Ms. Halie Choi, RegNet Environmental Services
Audrey Galizia USEPA
Bridget O'Brien USEPA
Dr. Resha M. Putzrath, Navy and Marine Corps Public Health Center
Ms. Laura A. Brust, American Chemistry Council
Dr. Kimberly Wise, American Chemistry Council

¹ Based on members of the public requesting the teleconference dial in information