United States Environmental Protection Agency (U.S. EPA)
Science Advisory Board (SAB) Quality Review
Teleconference Meeting
June 8, 2015
Meeting Minutes

Date and Time: June 8, 2015, 1:00 p.m. to 5:00 p.m.

Location: By teleconference only

Purpose: To review three draft SAB peer review reports on IRIS assessments: Ammonia, Trimethylbenzenes, and Ethylene Oxide.

Meeting Participants:

SAB Members (see Roster[1])

Dr. Peter Thorne, Chair
Dr. Sylvie M. Brouder
Dr. Thomas Burbacher
Dr. Ingrid Burke
Dr. George Daston
Dr. Costel Denson
Dr. Michael Dourson
Dr. Joel Ducoste
Dr. Elaine M. Faustman
Dr. H. Christopher Frey
Dr. Steven Hamburg
Dr. Cynthia M. Harris
Dr. Robert J. Johnston
Dr. Kimberly L. Jones
Dr. Nancy K. Kim
Dr. Francine Laden
Dr. Lois Lehman-McKeeman
Dr. Elizabeth Matsui
Dr. Eileen Murphy
Dr. James Opaluch
Mr. Richard L. Poirot
Dr. Amanda D. Rodewald
Dr. William Schlesinger
Dr. Gina Solomon
Dr. Daniel O. Stram
Dr. Paige Tolbert
Dr. Elke Weber
Dr. Charles Werth
Dr. Peter J. Wilcoxen
Dr. Dawn J. Wright

SAB Staff:
Mr. Thomas Carpenter, Designated Federal Officer (DFO), Chartered SAB and Chemical Assessment Advisory Committee (CAAC) augmented for the Review of Trimethylbenzenes
Mr. Christopher Zarba, SAB Staff Office Director
Dr. Suhair Shallal, DFO for the CAAC augmented for the Review of Ammonia
Mr. Aaron Yeow, DFO for the CAAC augmented for the Review of Ethylene Oxide

Other Attendees: Names of those who requested the teleconference call-in number are provided in Attachment A.

Meeting Materials:
All materials for the meeting are available on the SAB webpage at:
http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/17f305ec43eb1a6585257e2d0050255f!OpenDocument&Date=2015-06-08

Meeting Summary:

Convene the meeting

Mr. Thomas Carpenter, Designated Federal Officer (DFO) for the chartered SAB, formally opened the meeting and noted that this federal advisory committee teleconference of the SAB had been announced in the Federal Register[2] (Published May 12, 2015, 80 FR 27166-27167). The SAB is an independent, expert federal advisory committee chartered under the authority of the Federal Advisory Committee Act (FACA). The Environmental Research, Development, and Demonstration Authorization Act (ERDDAA) authorizes the SAB to provide advice to the EPA Administrator on scientific and technical issues that support the EPA's decisions. The DFO noted that the Federal Register notice announcing the meeting also provided the public with an opportunity to register and provide written or oral comment.

The DFO stated that the SAB consists of special government employees (SGEs) appointed by EPA to their positions. As SGEs, chartered SAB members are subject to all applicable ethics laws and implementing regulations. The SAB Staff Director has determined that advisors participating in this meeting have no financial conflicts of interest or appearance of a loss of impartiality under ethics regulations specified in 5 CFR 2635 relating to the topic of this meeting.

Purpose of the teleconference and review of the agenda

Dr. Thorne stated that the purpose of the teleconference is to conduct quality reviews for three peer reviews of IRIS assessments, ammonia, trimethylbenzenes (TMBs), and ethylene oxide. He briefly reviewed the agenda[3] and thanked SAB members for preparing comments for the quality reviews and their participation.

He called upon Dr. Vincent Cogliano, Director of the Integrated Risk Information System (IRIS) program, to provide opening remarks. Dr. Cogliano commented on the agency's effort to improve the IRIS program noting that the National Research Council (NRC) recently reviewed the program and noted substantial progress was made. Dr. Cogliano also identified some projects that may provide an opportunity for interaction in the future including an overview of issues raised in the SAB reports, an upcoming workshop on systematic review, and future CAAC meeting regarding the general charge questions on the NRC recommendations. He noted that the IRIS program has been working to further incorporate the NRC recommendations in assessments particularly in the preamble. Dr. Thorne thanked Dr. Cogliano for the remarks and asked the SAB members if there were any questions. Hearing none he proceeded with the agenda.

Dr. Thorne explained the process the SAB uses to reach a disposition for quality reviews. After the SAB discusses the report and member comments, in general, the chartered SAB may adopt the panel report (with agreed-upon revisions or corrections) subject to final review by the SAB chair, or subject to review by specified members of the chartered SAB. If necessary, the SAB may send the report back to the authoring panel for additional work, with a second quality review meeting to be scheduled to consider the revised report, or request that a new panel be formed to conduct the work.

Dr. Thorne noted that there were registered speakers for the reviews of the Trimethylbenzenes and Ethylene Oxide Assessments. No speakers registered to address the review of the Ammonia Assessment. The SAB quality reviews of the draft reports would begin with the public comments, questions from Board members on the public comments followed by a presentation of the panel chair and the SAB member's discussion.

Quality review of the draft SAB report, SAB Review of the EPA's Draft Toxicological Review of Ammonia (5/1/2015)

Presentation from the Panel Chair

Dr. Thorne noted that there were no registered speakers for the *SAB Review of the EPA's Draft Toxicological Review of Ammonia (5/1/2015)*[4] and introduced Dr. Michael Dourson, Chair of the SAB Chemical Assessment Advisory Committee (CAAC) augmented for the Review of the Ammonia Assessment. Dr. Thorne asked Dr. Dourson to provide an overview of the draft report as an introduction to the quality review discussion. Dr. Dourson acknowledged preliminary written comments received by chartered SAB members.[5]

Dr. Dourson noted the CAAC ammonia panel was a well-balanced peer review panel and consisted of CAAC members and additional disciplines including toxicologist, clinicians and chemists. He noted that IRIS assessments are hazard identification and dose response assessments and not risk assessments.

The panel identified some omissions that needed further explanation in the ammonia draft assessment. The document did not develop a reference dose (RfD) and the review recommends the agency provide clarification why data were insufficient to develop a RfD. The panel discussed ammonia chemistry and particularly endogenous ammonia. The panel recommended that the draft assessment include an introduction on ammonia chemistry to provide context. The panel agreed that there was insufficient data to develop a cancer value.

Regarding the reference concentration (RfC), the panel agreed with the agency's analysis and the use of Holness et al. (1989) as the critical study using the lower end of the range presented in Holness et al. The panel recommended that the agency contact the Holness authors and retrieve the individual exposure data.

Chartered SAB Discussion and Disposition of the Report

After Dr. Dourson completed his remarks, Dr. Thorne asked the lead reviewers to briefly summarize their written comments.

Dr. George Daston, the first lead reviewer on the call, noted that the charge questions were adequately addressed. The review is thorough and provides a number of constructive recommendations for each charge question. Dr. Daston commented that there are four general charge questions on how well the new IRIS format has complied with the NRC recommendations stemming from its 2011 formaldehyde review. Given that the charge questions

are the same in the ammonia and TMB reviews, the SAB should consider combining the responses from both reports into one set of consistent recommendations.

While the ammonia report supports the choice of Holness et al. as the critical study for establishing the inhalation RfC, the recommendation urges EPA to contact the authors of the study to request individual exposure data to determine whether an alternate point of departure could be calculated (i.e., could the conservative estimate be replaced with data). If these data are not forthcoming (which is a distinct possibility for a study published more than 25 years ago), does the panel's support for Holness as the critical study change?

Regarding the recommendation to extend the assessments discussion of exogenous ammonia it would be helpful to clarify the context of the recommendation. Is the purpose to better explain how exogenous ammonia is expected to be additive to endogenous ammonia, or is it to ground truth the RfC versus levels of endogenous ammonia that are associated (or not) with pathological conditions?

Dr. Francine Laden, the second lead reviewer agreed with Dr. Daston. She suggested that the responses to the charge questions for all the NRC recommendations could be separated from the respective assessments and presented in a single document about the NRC recommendations. She noted that the panel requested an updated review of the literature. Clearer guidance as to when the literature review should end should be provided.

Dr. Paige Tolbert, the third lead reviewer on the call, agreed with the previous comments and suggested the recommendations regarding the NRC recommendations could be clearer – particularly regarding whether to change the current assessment or modify the ongoing implementation of future assessments. She also agreed that the recommendation regarding the literature review needs to be clearer. Does the literature review need to be updated? The recommendation should clarify what is being requested; does the assessment need new papers that would change the assessment. Dr. Tolbert also suggested that the agency should consider the response to the questions regarding the implementation of the NRC recommendations from the two reviews as they revise each report rather than having the SAB or both panels continue to work on those recommendations.

Dr. Elizabeth Matsui joined the call during the discussion. As the fourth lead reviewer she provided written comments on the draft report.

Dr. Thorne thanked the lead reviewers for their comments. He then began the Board's general discussion and asked other members for comments.

Two members noted that the literature review is not being incorporated into a systematic review process and whether a systematic review is practical depends on EPA's plan and if the infrastructure to conduct systematic reviews is in place. Another members noted that it isn't clear if Appendixes B and C are consensus comments.

Dr. Dourson thanked members for their comments. He noted the panel discussed the range of the Holness et al. data and several options for the agency to address how to use these data if

individual data are not available. Regarding the endogenous ammonia the panel discussed sources of endogenous ammonia and concentrations of endogenous ammonia to ground truth the RfC. That is the RfC should not be a concentration greatly lower than the production of endogenous ammonia.

Dr. Dourson agreed with Dr. Tolbert that the NRC improvement related recommendations could be could be evaluated by the agency rather than the SAB taking on the compilation and discussion. He noted that the Chemical Assessment Advisory Committee intends to meet and discuss the implementation of the NRC recommendations. As to the literature review and timelines, Dr. Dourson believes that EPA has a literature review cutoff date that accounts for adding or reopening the literature review for assessments.

After discussion had concluded, Dr. Thorne proposed the three options to dispose the report. Dr. Tolbert moved that Drs. Dourson and Thorne work together to incorporate the recommended changes. Dr. Faustman seconded the motion. The motion was approved unanimously with no abstentions.

Quality review of the draft SAB report, Science Advisory Board Review of the IRIS Draft Toxicological Review of Trimethylbenzenes (5/1/2015)

Dr. Thorne noted that there were two speakers registered to provide comment on the S*AB Review of the EPA's Draft Toxicological Review of Trimethylbenzenes (5/1/2015)*[6] and proceeded with the agenda.

Public comments

Dr. Nancy Beck, American Chemistry Council[7] and Dr. Moyinoluwa David Adenuga, Hydrocarbon Solvent Panel American Chemistry Council[8] addressed the SAB regarding the review of the TMB assessment. Dr. Beck noted the lack of consensus in recommendations regarding uncertainty factors (UFs) and commented that the report should not be approved in its current state. She also noted that there was not unanimity on the role of the C-9 fraction and reversibility of pain sensitivity data. Dr. Beck asserted that the lack of consensus on these issues was of sufficient concern for the SAB to return the draft report to the panel to reach consensus on these issues.

Dr. Adenuga presented information on an Office of Pesticide Program (OPP) rule exempting C-9-rich aromatic hydrocarbons (asserting the mixture is essentially the same substance as the TMB isomers) from the requirement of a tolerance. The final rule was published by the EPA's Office of Pesticide Programs (OPP) in the Federal Register on September 26, 2014 (79 Fed. Reg. 57805) and he noted that the OPP developed RfD value of 1.5 mg/kg/day, a value that is at least 2 orders of magnitude higher than the values proposed in the IRIS assessment of TMB and asked the SAB to recommend that EPA return to the drawing board to understand why there is such a huge disparity in the IRIS and OPP assessments of practically the same substances. Dr. Thorne thanked the commenters and asked if members had any clarifying questions. Hearing none he proceeded with the agenda.

Presentation from the Panel Chair

Dr. Thorne introduced Dr. Cynthia Harris, Chair of the SAB CAAC augmented for the Review of the Trimethylbenzenes Assessment. Dr. Thorne asked Dr. Harris to provide an overview of the draft report as an introduction to the quality review discussion. Dr. Harris then acknowledged preliminary written comments received by chartered SAB members.[9]

Dr. Harris noted the SAB was asked to review the scientific and technical analyses used to develop reference concentrations (RfC) and reference doses (RfD) for the three TMB isomers and to comment on the agency's enhancements made to the IRIS Program in response to the NRC recommendations. She noted that the EPA developed the values for the individual isomers because they were detected at superfund sites as described in the executive summary of the SAB report. The panel had two tasks, (1) to review the scientific and technical aspects of the TMB assessment and (2) comment on EPA's progress to enhance the presentation of their analysis

Overall, the TMB panel agreed with the agency approach and found using a physiologically based pharmacokinetic (PBPK) modeling approach and extrapolating inhalation data to an oral exposure as appropriate for the reference concentration and reference dose for 1,2,3-TMB, 1,2,4-TMB and 1,3,5-TMB. There was consensus on using Korsak and Rydzynsky (1996) as the critical study for the RfC and RfDs. The panel agreed that EPA could not conduct a quantitative cancer assessment for any of the TMB isomers due to the lack of appropriate studies.

She noted the panel discussed the issues raised by some of the SAB the members and public comments. For example the use of data for closely related compounds (i.e., C-9 fraction and other alkylbenzenes) and when the agency should include these types of data. Generally the panel found that these types of data should be used qualitatively and to fill data gaps. The panel also was aware of the OPP C-9 fraction RfD and found that these and other C-9 data did not provide a surrogate for the individual TMB toxicity data. This assessment is focused on the exposure to the TMBs and the panel found the C-9 fraction should not be compared directly to the TMB studies. The panel members generally agreed that the UFs for each of the isomers should be consistent. There was discussion for the five UFs and the discussion is accurately reflected in the draft report. Where there are difference in the UF discussion among panel members the agency may evaluate the discussion and apply the agency's guidance on UFs in a transparent manner.

Chartered SAB Discussion and Disposition of the Report

After Dr. Harris completed her remarks, Dr. Thorne asked the lead reviewers to briefly summarize their written comments.

Dr. George Daston, the first lead reviewer on the call and found the review to be thorough and provides a number of constructive recommendations for each charge question. It would be helpful to clarify the recommendations about PBPK modeling for the TMB assessment and any future use of PBPK modeling. There appears to be inconsistent advice on the use of a structure-activity approach using related compounds to fill data gaps. Some of the advice seems to be encouraging, while elsewhere the report suggests that this would just be replacing one

uncertainty (about database completeness) with another (extrapolation across chemicals). It is not clear why this was suggested for non-cancer endpoints but not to cover data gaps for carcinogenicity.

Dr. Nancy Kim, the second lead reviewer on the call, found the report is well done, responds to the charge questions, and is well written. In a few places some clarification or rewriting would help. She agreed with Dr. Daston's remarks and sections that could be clarified in the report.

Dr. Lois Lehmann-McKeeman, the third lead reviewer thanked Dr. Harris for her overview. She agreed with Dr. Daston's comments and found the report lacked clarity and the logic regarding the C-9 analogs. She also found the review of the PBPK modeling in Appendix B to be thorough.

Dr. Thorne thanked the lead reviewers for their comments and noted that Dr. Harris addressed many of the lead reviewers' comments in her overview. Dr. Harris thanked the lead reviewers and noted that she believed their comments could be addressed with revisions to the report. She noted that the comments for clarity in the recommendation can be addressed, particularly the use of analogs and PBPK modeling recommendations.

Dr. Thorne asked other members of the SAB if they had any additional comments. One member noted that he appreciated the discussion on uncertainty factors and the development of less than life time (subchronic) toxicity values. He asked about the OPP Tolerance exemption and if they may be in conflict with the IRIS Assessment. Mr. Kerry Liefer from the OPP was on the teleconference and explained OPPs approach and noted differences in the respective programs goals, endpoints considered and disagreement in neurotoxicology between the isomers and mixture studies. Allen Davis National Center for Exposure Assessment noted that OPP only considered Douglas et al. (1993) in developing their tolerance exemption and not the same set of studies considered in the IRIS assessment and this may be the cause of the discrepancy between the TMB isomers and mixture data. Mr. Allen noted that the SAB review of the TMB report recommends additional analysis of the mixture and TMB isomer data to better clarify the different results.

After discussion had concluded, Dr. Thorne asked for a motion to dispose of the report. He reviewed the three options and asked for a motion. Dr. Faustman proposed that Drs. Harris and Thorne revise the report. Dr. Kim seconded the motion and called for a vote. Dr. Dourson asked that there should be a clear communication on the difference between the OPP and IRIS analyses. Dr. Thorne thought the discussion on the call would convey Dr. Dourson's concern.

The motion was approved unanimously. There were no abstentions.

Quality review of the draft report, Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (April 27, 2015)

Dr. Thorne stated that he was the Chair of the CAAC Augmented for the Review of Ethylene Oxide and called upon Dr. Nancy Kim who agreed to chair the Quality Review of the *Draft Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (April 27, 2015)*[10] Dr. Kim introduced the three registered speakers for this agenda item.

Public Comments

Dr. Nancy Beck, American Chemistry Council[11], Mr. Bill Gulledge of the American Chemistry Council's Ethylene Oxide Panel[12] and Mr. Jake Vandervort, Ethylene Sterilization Association, Inc., addressed the SAB regarding the review of the ethylene oxide assessment. Dr. Beck commented that the ethylene oxide assessment needs sensitivity analyses, a new approach to linear modeling (using individual data over categorical), the uncertainty discussion needs improvement and extension, and the clarity and interpretation of findings relating to genotoxicity need revision as per the many detailed suggestions in the report. She also noted that these analyses would to benefit from appropriate levels of public comment and peer review. She also asked for more clarification of the use of the National Institute of Occupational Safety and Health (NIOSH) cohort over the Union Carbide Corporation (UCC) data.

Mr. Gulledge informed the SAB that public comments were provided to the Ethylene Oxide Panel and these comments would be useful to EPA in addressing the SAB recommendations. A listing of those comments is included in his written statement.

Mr. Vandervort noted that he agreed with the previous presentations and also noted that the draft IRIS Assessment needs additional work. He encouraged the SAB members to further consider the public comments submitted on the 2013 IRIS Assessments and those submitted to the CAAC Ethylene Oxide Panel. He encouraged the SAB to recommend the agency consider the UCC data and not solely rely on the NIOSH data set. He also urged the SAB to recommend that the IRIS Assessment be revised and made available for public comment before being submitted for final interagency review.

Presentation from the Panel Chair

Dr. Kim thanked the public commenters and asked Dr. Thorne to provide an overview to the draft report.

Dr. Thorne noted that the CAAC Augmented for the Review Ethylene Oxide included experts in the fields of biostatistics, toxicology, carcinogenicity, and risk assessment. The panel met at a three day face-to-face meeting and held two teleconferences. He noted that the panel heard over two hours of public comments for consideration at these meeting in addition to receiving their written comments. He also pointed out that the SAB provided advice on ethylene oxide in 2007 and the agency's 2014 draft assessment addressed many of the same recommendations from the public.

The charge questions to the Ethylene Oxide Panel address latency and exposure lagging issues, the slope of predicted cancer incidence the models predict at low dose ranges, the quality of the available data sets, and the EPA's response to public comments to a 2013 version of the assessment. The panel found that the literature review was complete and agreed with the agency's use of the NIOSH study as the most appropriate study. He stated that a better description should be included of the data available in Steenland et al. (2003, 2004) and Hornlund et al. (1994). He noted that the panel discussed the UCC data and identified significant flaws including small sample size, multiple confounding exposures to additional chemicals, and that the categorical exposure presents an opportunity for misclassification.

The recommendations of the panel support lagging exposure estimates and a strong relation of latency and noted the key issue is selecting the proper length of the latency period. The report recommends conducting sensitivity analyses to evaluate the latency lagging period. The panel found that the evidence for a mutagenic mode of action was strong. He noted that the assessment used complex biostatistics and epidemiology. They agreed with two-piece spline model and noted that the model fit at low doses was consistent with consideration of biological plausibility. The discussion of the Akaike information criterion (AIC) recommended changes in how the agency used the AIC.

Chartered SAB Discussion and Disposition of the Report

After Dr. Thorne completed his remarks, Dr. Kim asked the lead reviewers to briefly summarize their written comments.

Dr. Thomas Burbacher, the first lead reviewer on the call, commented that the charge questions to the committee were adequately addressed, although there are a few areas where he suggested improvements. He noted that the letter to the Administrator should include more of the recommendations. He noted the study date and that the NIOSH data may not be available.

He suggested that a summary of recommendations be provided for charge question 1. It is not clear from the comments regarding the CDC 9-11 Working Group Guidelines and the sensitivity analysis recommendations what is being requested of the agency. Summary recommendations were provided for the other charge questions and it was very helpful.

The panel recommended using a model based on individual-level exposure data rather than the use of categorical results as the preferred model for derivation of the (low exposure) unit risk estimate for lymphoid cancer. Adding a summary of the key issues to the report and indicating why individual level exposure data is a better approach would be helpful to EPA.

In addition, it would be helpful to indicate that there is support for the EPA's selected model for breast cancer at the beginning of the section for charge question 2, given the extensive discussion of other approaches that is included in this section.

Dr. Gina Solomon, the second lead reviewer on the call, commented on that the report read clearly and the key issues were conveyed in the cover letter and executive summary. She noted two issues that she thought lacked clarity. For example, the report should provide more detail on

why the UCC study was not included based on standard mortality ratios, the panel needs to clearly state this is an issue with occupational studies and bias that is introduced toward the null is valid but not clearly stated in the report.

She noted the response to question 2b is extremely clear and well-written, and the discussion of the AIC on p, 14 is much clearer than in question 2a. Perhaps this discussion could be referenced in the earlier section? She also noted there was a good discussion on mutagenic mode of action (MOA) and reasoning for linear dose response in the review in contrast to the statements by the public commenters.

Dr. Daniel Stram, the third lead reviewer commented that the SAB review has been extensive and that the charge questions have been addressed fully. The SAB review expresses preference for models that are sensitive to the local behavior of the data so that the estimate of response to low exposures is not unduly influenced by the estimate of high exposure response. While this preference may be ideal, the available data may be too limited to meet this recommendation. He found that a fall back of an assumption of linearity for a mutagenic exposure, seems useful for estimating low-exposure effects, since the low exposure data itself may be too limited to distinguish between the various models considered. He noted that the review correctly indicates that sensitivity analyses on lagging periods should be performed. The choice of a lag period for a mutagenic outcome should in principle be based upon an assessment of the amount of time required for a detectable cancer to develop from a damaged single cell; such an assessment would benefit from contributions from a variety of epidemiological and laboratory studies and not simply be based on empirical fitting to the single dataset being considered.

Dr. Stram agreed with Dr. Burbacher regarding the NIOSH exposure estimates. The SAB review makes some very reasonable recommendations to EPA including obtaining the exposure estimates from NIOSH and providing tables and figures of the distribution of predicted exposures in the NIOSH dataset, as well as summaries of exposures and other relevant variables for cases and controls. A key issue is whether allowance for exposure uncertainty especially for the earlier time periods should affect the interpretation of the apparent non-linearity in response seen especially for lymphoid cancer. The Ethylene Oxide Panel reviewers identified the key uncertainties in their report. However the Mickoczy study may be more contradictory to the NIOSH study than complimentary to reduce uncertainty.

Dr. John Vena, the forth lead reviewer commented that the report was comprehensive and thorough. Explicit recommendations are made after very well written responses to the questions, thoughtful critique of the assessment document and justification for the recommendations that follow. He agrees with the previous reviewers and notes that there are a few sections where language can be clarified and these are noted in his written comments. He suggested the heading in question 4 could be reworded. He also suggested reworking the letter to the Administrator and the body of the report regarding the Mickozy et al. study. In the Executive Summary, the report should clarify how Mickozy et al. supports the recommendation to use the NIOSH study.

Dr. Kim thanked the lead reviewers for their comments and asked Dr. Thorne to address the reviewers' comments.

Dr. Thorne noted that he thought the reviewers comments could be readily addressed and offered some options and clarifications.

The "Mickozy et al. (2011)" and the "Swedish Study" reviewers are mentioning are the same study. Regarding the UCC concerns, the hazard identification discussion in the IRIS assessment articulated the reasons not to use the UCC study. The panel agreed with this presentation and didn't think it necessary to repeat the analysis in the review. Given the reviewers comments, the revision can incorporate some of that discussion.

The Mickoczy et al. study had the best exposure work that has been done and included good ascertainment of exposure and cases. In looking at the four categorical groups at the low dose end of the exposure range the panel thought the support by Mickozy et al. would corroborate that low-doses of ethylene oxide could have produced the observed cases of breast cancer.

Dr. Thorne noted that Dr. Burbacher summarized the individual versus categorical data issue well. Dr. Thorne agreed with reviewers that the NIOSH dataset could be better explained. He noted that the NIOSH data are well explained in Steenland et al. (2003, 2004) and Hornung et al. (1994). There are individual dose data in these publications, but they are based on job exposure matrices and modeling of the data because in the early years there was exposure assessment by area within a plant (this was in 14 different facilities). Modeling was for each individual worker over their working life history. The modeled data are still available and are summarized in publications. However, the raw data on individuals that went into those earlier exposure assessments are no longer available. What the Ethylene Oxide Panel suggested is to include a table of descriptive data, just to introduce and describe the data to add clarity.

Dr. Thorne thought the lead reviewers comments could be addressed in the SAB report by better stating the appropriate use of the AIC and harmonizing paragraphs. He also thought the panel discussed the local behavior of the data with exposure to ethylene oxide only, low dose steepness, mutagenic action, and lagging concurrence and reviewers comments could be addressed.

Dr. Kim asked other SAB members if they had any additional comments and recognized Dr. Dourson.

Dr. Dourson commented that he had three suggestions or recommendations for the SAB to consider.

- He asked if the panel discussed temporal concordance and temporal sequence? He noted the importance of the MOA in EPA's framework and suggested that oxidative stress, mutations, and then tumors may be an alternate MOA. He believed that this point was important because the current EPA guidelines would require the agency to model both MOAs or consider a threshold approach. His recommendation was for the SAB report to recommend or maybe suggest that EPA conduct a dose-response concordance analysis.
- Did the panel consider endogenous ethylene oxide and compare the endogenously off-gassed ethylene oxide to the agency estimate?
- Did the panel discuss biological uncertainty in the discussions?

Dr. Thorne responded that sequencing was discussed in the context of MOA and dose ranges. He noted that public commenters also provided information on this issue. Drs. Ken Ramos and Gary Ginsberg were on the panel and led these discussions. He noted that the panel found the pattern fit a mutagenic MOA and discussed dose-response concordance from epidemiologic studies. He recollected that the animal study data suggested that the tumors from oxidative stress were happening at higher doses than the adducts which would occur first with early exposure. Dr. Thorne offered to confer with the lead discussants to make sure that the temporal sequencing was addressed.

Regarding endogenous ethylene oxide the panel found that EPA's response was appropriate, that the background rates for cancer had been taken into account in the risk estimate, and this would account for the endogenous ethylene oxide production, which is very low. Biologic plausibility was also discussed. The panel recommended the agency conduct a sensitivity analysis and ask for clarity of the biological plausibility. So the panel is largely in agreement with you on that point.

After discussion had concluded, Dr. Kim proposed several options to finalize the report. 1) As the member presiding the quality review, she and Dr. Thorne would review the revisions and finalize the report, 2) The chairs and lead reviewers would review the Report, and 3) the chairs and a group of self-selected SAB members would review the revisions.

Dr. Dourson moved for the report to be finalized by a group of SAB Members including the chairs (option 3). Dr. Faustman simultaneously moved to have the chairs revise the report (option 2). Dr. Solomon seconded Dr. Faustman's motion. Dr. Dourson then requested an amendment to the motion adding an additional person to the group revising the report.

A point of clarification was requested to define the motion under discussion. The DFO restated that two motions were made. Dr. Dourson's motion was made first but there was not a call for a second. Dr. Faustman's proposed alternative motion was seconded. Dr. Dourson agreed to discuss the motion made Dr. Faustman and possible amendments, that the report be revised and reviewed by the presiding chair and chair of the CAAC Ethylene Oxide Panel.

Members discussed the expertise on the Ethylene Oxide Panel and the proposal to confer with the carcinogenicity experts regarding temporal sequencing and dose concordance issues. Dr. Solomon asked what additional expertise (i.e., modeling or carcinogenicity) requires an additional SAB member to assist the acting SAB chair and the panel chair. Dr. Dourson responded he would like to make sure that a member familiar with the carcinogenic MOA and the EPA 2005 guidance and dose concordance. Dr. Thorne suggested that in Drs. Ramos and Ginsberg provide the requested expertise. Dr. Faustman suggested that the SAB ask the chairs to address dose concordance and work with the panel members with the requested expertise. Dr. Denson called the question to vote on the motion. Dr. Burke seconded the call for the vote on this motion. The motion to vote was approved unanimously.

Dr. Kim asked for the yeas and nays on the motion for Drs. Kim and Thorne to revise the SAB Review of the Ethyene Oxide IRIS Assessment after consultation with carcinogenicity experts on the CAAC Augmented for the Review of Ethylene Oxide regarding temporal sequencing and

dose concordance issues. The motion was approved by voice vote with no nays and one abstention.

The DFO adjourned the meeting at 4:15 p.m.

Respectfully Submitted	Certified as Accurate
____/signed/_____	___*/signed/*_____
Dr. Thomas Carpenter	Dr. Peter S. Thorne
SAB DFO	SAB 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 to not rely on the minutes to 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: Names of those who requested the teleconference call-in number

Mr. Allen Davis, US Environmental Protection Agency (EPA)
Mr. Steve Dutton, US EPA
Dr. Vince Cogliano, US EPA
Dr. Samantha Jones, US EPA
Dr. Bob Sonawane, US EPA
Dr. David Bussard, US EPA
Dr. Norm Birchfield, US EPA
Ms. Sue Rieth, US EPA
Ms. Mary Ross, US EPA
Ms. Jennifer Jinot, US EPA
Mr. Andrew Kraft, US EPA
Mr. Jenny Li, US EPA
Ms. Audrey Galizia, US EPA
Mr. Ted Berner, US EPA
Dr. Lynn Flowers, US EPA
Ms. Laura Dishaw, US EPA
Mr. Kerry Liefer, US EPA
Mr. Dahnish Shams, Student Services Contractor to EPA
Mr. Naseera Bland, Student Services Contractor to EPA
Mr. Jim Kim, Office Information and Regulatory Affairs, Office of Management and Budget
Mr. Bill Gulledge, American Chemistry Council (ACC)
Ms. Laura E. Boorman, Esq. |Venable LLP
Gary M. Marsh, Ph.D., F.A.C.E., University of Pittsburgh
Mr. Kevin Bromberg, Small Business Administration
Ms. Maria Hegstad, Inside EPA
Mr. Jake Vandervort, B & C Consortia Management, LLC
Lynn H. Pottenger, Ph.D., D.A.B.T. The Dow Chemical Company
Dr. Nancy Beck, ACC
Mr. Jon Busch, ACC
Dr. Resha Putzrath, United States Navy
Ms. Patricia Rizzuto, Bloomberg BNA

Materials Cited

The following meeting materials are available on the SAB website, http://www.epa.gov/sab, at the page for the June 8, 2015 teleconference: http://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/17f305ec43eb1a6585257e2d0050255f!OpenDocument&Date=2015-06-08

[1] Roster of SAB members

[2] Federal Register published Vol. 80, No. 80 Monday, April 27, 2015 (23271-23272)

[3] Draft Agenda U.S. Environmental Protection Agency Science Advisory Board (SAB) Teleconference June 8, 2015

[4] Draft SAB Review of the EPA's Draft Toxicological Review of Ammonia (5/1/2015)

[5] Comments from Members of the Chartered SAB on the SAB Draft Report: SAB Review of the EPA's Draft Toxicological Review of Ammonia (5/1/2015)

[6] Draft SAB Review of the EPA's Draft Toxicological Review of Trimethylbenzenes (5/1/2015)

[7] American Chemistry Council Oral Comments to the Chartered SAB Quality Review of the Draft Report on EPA's Toxicological Review of Trimethylbenzene

[8] American Chemistry Council Hydrocarbon Solvents Panel Oral Comments to the Chartered SAB Quality Review of the Draft Report on EPA's Toxicological Review of Trimethylbenzene

[9] Comments from Members of the Chartered SAB on the SAB Draft Report: Science Advisory Board Review of the IRIS Draft Toxicological Review of Trimethylbenzenes (5/1/2015), List of comments received as of June 2, 2015. (PDF, 15 pp., 126,511 bytes)

[10] Draft Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (April 27, 2015)

[11] Public statement from Nancy Beck, PhD, DABT, on behalf of the American Chemistry Council, to the Chartered Science Advisory Board regarding the Chemical Assessment Advisory Committee (CAAC) review of the Draft Ethylene Oxide (EO) IRIS Assessment.

[12] Public statement from Bill Gulledge on behalf of the American Chemistry Council's Ethylene Oxide Panel to the Chartered Science Advisory Board regarding the Chemical Assessment Advisory Committee (CAAC) review of the Draft Ethylene Oxide (EO) IRIS Assessment.