U.S. Environmental Protection Agency
Science Advisory Board
Chemical Assessment Advisory Committee (CAAC)
Augmented for the Review of Ethyl Tertiary Butyl Ether (ETBE)
***and* tert-Butyl Alcohol (tBA)**

Public Meeting
August 15-17, 2017

Minutes of the Meeting

Location: Residence Inn Arlington Capital View, 2850 S Potomac Ave, Arlington, VA 22202.

Purpose:
The purpose of the meeting was to conduct a peer review two EPA draft assessments: 1) Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE) and 2) Toxicological Review for tert-Butyl Alcohol (tert-butanol or tBA).

Participants:

Augmented CAAC for ETBE/tBA Members:

Dr. Janice E. Chambers (CHAIR)
Dr. Hugh A. Barton
Dr. Janet Benson
Dr. Trish Berger
Dr. James Bruckner
Dr. John Budroe
Dr. Karen Chou
Dr. Harvey Clewell
Dr. Deborah Cory-Slechta
Dr. Bevin Engelward
Dr. Jeffrey Fisher
Dr. William Michael Foster
Dr. Alan Hoberman
Dr. Tamarra James-Todd
Dr. Lawrence Lash
Dr. Marvin Meistrich
Dr. Maria Morandi
Dr. Isaac Pessah*
Dr. Lorenz Rhomberg
Dr. Stephen M. Roberts
Dr. Alan Stern

*Participated via teleconference

SAB Staff:
Dr. Shaunta Hill-Hammond, Designated Federal Officer (DFO) for the Augmented CAAC for ETBE/tBA
Mr. Christopher Zarba, Director, SAB Staff Office
Dr. Sue Shallal, SAB Staff Office

Other Attendees: See Appendix A.

Meeting Summary:
The meeting occurred from August 15 – 17, 2017. The discussion followed the topics as presented in the meeting agenda.[i]

Tuesday, August 15, 2017

Opening of Public Meeting:
Dr. Shaunta Hill-Hammond, the Designated Federal Officer (DFO), convened the meeting with a statement reminding the audience that CAAC augmented for the review of ETBE and tBA (hereafter referred to as the CAAC-ETBE/tBA Panel or Panel), operates under the Federal Advisory Committee Act (FACA). Under FACA, Dr. Hill-Hammond noted that the SAB's deliberations are held in public with advanced notice given in the Federal Register.[ii] The SAB consists entirely of special government employees appointed by EPA to their positions. As special government employees, all the members are subject to all applicable ethics laws and implementing regulations.

Dr. Hill-Hammond stated that for this SAB advisory activity, no conflict of interest or loss of impartiality issues were identified for any Panel member. She then reminded all participants that the meeting materials were available on the SAB website. Mr. Christopher Zarba, Director of the SAB Staff Office, welcomed and thanked members for their willingness to serve on this panel. Dr. Janice Chambers, Chair of the CAAC-ETBE/tBA Panel followed, offering welcoming remarks and inviting Panel members to introduce themselves. She then reviewed the meeting agenda and invited the EPA representatives to begin their presentations.

EPA Presentations:
Dr. Keith Salazar of the EPA National Center for Environmental Assessment, presented on the ETBE assessment.[iii] His presentation[iv] highlighted the development of the ETBE assessment, including general information on the chemical, implementation of the NRC[1] recommendations in the assessment, and an overview of the toxicological reviews conducted. Dr. Salazar also provided a summary of questions received from the Panel during the July 11, 2017 teleconference and provided a recap of the EPA's verbal responses.

Dr. Janice Lee, of the EPA National Center for Environmental Assessment, presented on the tBA assessment.[v] Her presentation[vi] highlighted the development of the tBA assessment, including general information on the chemical, implementation of the NRC recommendations in the assessment, and an overview of the toxicological reviews conducted. In closing, Dr. Lee provided a summary of questions received from the Panel during the July 11, 2017 teleconference and provided a recap of the EPA's verbal responses.

Dr. Chambers thanked the EPA presenters and turned the meeting over to Dr. Hill-Hammond for the facilitation of public comments.

[1] NRC (National Research Council). 2011. Review of the Environmental Protection Agency's draft IRIS assessment of formaldehyde (pp. 194). Washington, DC: The National Academies Press.

Public Comments:
Seven individuals registered to present oral comments.[vii] Comments were organized by chemical. Dr. Hill-Hammond invited each commenter to present their statements.

ETBE:
Dr. Fukumi Nishimaki of the Japan Petroleum Energy Center, presented[viii] several proposed revisions for the ETBE assessment relating to the carcinogenicity potential and mode of action.

Dr. Shoji Fukushima of the Japan Bioassay Research Center on behalf of Japan Petroleum Energy Center, presented[ix] information illustrating a proposed mode of action for ETBE hepatotumorigenicity in rats. She also highlighted that the available mode of action data were adequate for the assessment of ETBE's tumorigenicity and that liver tumors induced by ETBE are not relevant to humans.

Dr. James Bus of Exponent presented comments on behalf of LyondellBasell. His comments were specific to the proposed cancer classification for ETBE and the low concern for human health impacts by inhalation and oral exposures.

Dr. Samuel Cohen of the University of Nebraska Medical, presented[x] comments focused on the relevance of effects to human health. Specifically, he noted that the kidney rat tumor and liver rat tumor findings were not relevant to humans, while the centrilobular hypertrophy findings in rat liver were potentially relevant to humans.

Dr. Katy Goyak of ExxonMobil Biomedical Sciences, Inc. on behalf of the American Petroleum Institute (API), presented comments relating to the cancer classification, the cancer risk quantification, and the critical endpoint chosen for noncancer risk assessment of ETBE.

tBA:
Dr. Marcy Banton of LyondellBasell shared comments regarding the proposed cancer classification for tBA and the low human health risk by inhalation and oral exposures. She highlighted specifically that tumors were only present at high does and stated that critical analysis of the Melnick et al. papers[2,3] was needed.

Dr. Cohen's comments[xi] focused on the relevance of effects to human health. Specifically, he noted that all findings in kidneys in tBA studies were due to alpha-2μ globulin ($\alpha_{2\mu}$-globulin) nephropathy, chronic progressive nephropathy (CPN) and cortico-medullary calcification and that none of those factors were relevant to humans.

Dr. Goyak presented comments relating to the cancer classification, the cancer risk quantification, and the critical endpoint chosen for noncancer risk assessment of tBA.

[2] Melnick, R; Burns, K; Ward, J; Huff, J. 2012. Chemically exacerbated chronic progressive nephropathy not associated with renal tubule tumor induction in rats: An evaluation based on 60 carcinogenicity studies by the National Toxicology Program. Toxicol Sci. 128: 346-356.
[3] Melnick, RL; Ward, JM; Huff, J. 2013. War on carcinogens: Industry disputes human relevance of chemicals causing cancer in laboratory animals based on unproven hypotheses, using kidney tumors as an example [Editorial]. Int J Occup Environ Health. 19: 255-260.

The final public commenter was Kevin Bromberg who presented comments on behalf of the U.S. Small Business Administration, Office of Advocacy. Mr. Bromberg proposed revisions to the charge questions, suggested that EPA seek the expert advice of pathologists to assess the kidney effects highlighted in both assessments and requested transparency with respect to the scoring of individual studies selected for the assessments.

Discussion of the Charge Questions:
Following public comments, Dr. Chambers led the review of the charge questions.[xii] Dr. Chambers read each charge question and asked for comments from the members of the assigned sub-group and then the members of the full Panel.

1. Literature Search Strategy/ Study Selection and Evaluation- Systematic Review Methods Study Selection and Evaluation

ETBE:
Overall, the Panel agreed that the search strategies, criteria for study inclusion/exclusion and evaluation and for study quality were described clearly. The Panel also agreed that the search strategies likely captured all the relevant key studies. The Panel noted that the approach to the search did not adhere strictly to the NRC recommendations and EPA should provide a clarification. The Panel also identified some inconsistencies with dates selected for the literature search updates across sources, as well as, literature source limitations in the manual searches for additional relevant citations.

Panel members were not able to determine how studies were objectively judged for quality based on the classification and quality criteria. The Panel stated that there is no documentation on decision making for each of the studies. They noted that EPA should provide documentation about this process, perhaps as part of the HERO database.

tBA:
The Panel drew the same conclusions for tBA as stated for ETBE.

2. Hazard Identification and Dose-Response Analysis

ETBE:
2a. Chemical properties
The Panel noted several inconsistencies between the chemical property data provided in Table 1-1 of the assessment and the values reported in the cited sources. Additionally, some values included in Table 1-1 did not include citations for references. Specific items mentioned for revision included water solubility, log octanol:water partition coefficient, and odor recognition in water.

The Panel also noted that if more than one value is found in primary peer-reviewed sources, that EPA should provide a rationale for the value chosen for presentation/inclusion in the assessment. Further, it was suggested that EPA should limit primary peer-reviewed sources to original data

sources and not reviews of original sources or other government documents. The Panel then suggested that EPA develop a template for future assessments to focus on listing only the relevant chemical properties.

2b. Toxicokinetic modeling

The Panel agreed that EPA's application of the PBPK model for ETBE, including the tBA submodel, in the dose-response characterization of ETBE was an appropriate way to incorporate science using state-of-the-art methods. For purposes of using physiologically-based pharmacokinetic (PBPK) models in IRIS assessments, the Panel agreed that EPA needs to establish a consistent practice for documenting both the model itself and the review of the model (and any modifications made by EPA to implement it). The Panel also noted that the overall presentation of the PBPK modeling should be more cohesive, clear, and transparent. Providing essential information, assumptions, results and conclusions within the assessment would be most helpful, as noted by the Panel.

2c. Choice of dose metric

The Panel agreed that the rate of metabolism should not be used as the dose metric for extrapolation from inhalation to oral routes of administration. The Panel highlighted that there was no "consistent dose-response relationship" for the dose metric dose, when combining oral and inhalation studies to assess liver tumors. No other dose metrics were identified that would work better for route extrapolation of the liver cancer endpoint. The Panel recommended that the EPA not implement route extrapolation for the oral cancer dose-response analysis.

tBA:

2a. Chemical properties

The Panel raised points similar to those for ETBE. Several inconsistencies were noted between the chemical properties data provided in Table 1-1 of the assessment and the values reported in the cited sources. Additionally, some values included in Table 1-1 did not include citations for reference. Specific items mentioned for revision included log octanol: water partition coefficient, melting and boiling points, and density/specific gravity.

2b. Toxicokinetic modeling

The Panel suggested that the descriptions of dose metrics in text and figures be corrected to reflect the fact that the dose metric is the average concentration of tBA in the blood after periodicity is achieved. The Panel agreed that the material in US EPA (2017)[4] should be included in Appendix B of the Supplemental Information document[5] or as a separate appendix. The Panel agreed that EPA could give additional consideration to modifying the model of Nihlen and Johanson (1999)[6] to support cross-species extrapolations for both inhalation and oral routes of exposure.

[4] U.S. EPA. 2017. PK/PBPK model evaluation for the IRIS assessments of ethyl tertiary butyl ether (CASRN 637-92-3) and tert-butyl alcohol (CAS No. 75-65-0) (Draft).

[5] U.S. EPA. 2017. Toxicological Review of tert-Butyl Alcohol (tert-Butanol) (CASRN 75-65-0). Supplemental Information.

[6] Nihlén, A; Johanson, G. 1999. Physiologically based toxicokinetic modeling of inhaled ethyl tertiary-butyl ether in humans. Toxicol Sci. 51: 184-194.

2c. Choice of dose metric

The Panel agreed that the average concentration of tBA in blood was an appropriate choice for the dose metric as there is a dose-response relationship for the dose metric and a kidney non-cancer endpoint. With that, the Panel recommended an oral to inhalation route-to-route extrapolation. The Panel noted that inter-species extrapolation can be conducted based on the human inhalation PBPK model for ETBE and tBA (Nihlen and Johanson, 1999) thereby avoiding a default human equivalent dose calculation.

3. Hazard Identification and Dose–Response Assessment: Noncancer

ETBE:

3a. Noncancer kidney toxicity

The Panel agreed that 1) the conclusion was clearly described but disagreed about whether it was scientifically supported; 2) the explanation that absolute kidney weight is a more reliable reflection of specific effects on the kidneys was clearly explained and scientifically supported; and 3) the $\alpha_{2\mu}$-globulin effects and their role in explaining renal tumors in male rats is presented in a thorough and systematic manner according to established EPA Guidelines.

Considerable discussion with divergent viewpoints occurred with respect to how the ETBE database for noncancer kidney effects should be interpreted, with no clear consensus reached. Some Panel members agreed with the overall interpretation and conclusion presented in the assessment. One member noted in particular that the focus of the ETBE assessment should be on public health and that considerations should be conservative and consider potential human relevance to protect human health. Thus, the conclusions of the EPA were reasonable and appropriate. Others Panel members concluded that there was limited evidence to support the human relevance of noncancer kidney effects in rats.

The Panel did note a couple of recommendations. Specially, EPA should apply more detailed criteria such as those used by IARC (1999)[7] in consideration of the role of $\alpha_{2\mu}$-globulin in ETBE-induced nephropathy in male rats. EPA could also consider the use of another parameter, such as an increase in blood (serum) biomarkers or exacerbation of nephropathy, instead of urothelial hyperplasia, as a surrogate for noncancer kidney effects.

3b. Noncancer toxicity at other sites

The Panel supported the use of the kidney effects (urothelial hyperplasia observed at 170 mg/kg-d, 6,000 mg/m3) as opposed to liver effects for deriving reference doses. To characterize the developmental toxicity of ETBE, the Panel suggested that "minimal effects at otherwise toxic dose levels" rather than "inadequate evidence" should be used.

3c. Oral reference dose (RfD) for noncancer outcomes

The Panel did not reach consensus on the scientific support to determine the appropriateness of using kidney effects as the endpoint (3a) for deriving an RfD. When kidney effects are considered to be the appropriate endpoint, the Panel found that the derivation was appropriate

[7] IARC (International Agency for Research on Cancer). 1999. Some chemicals that cause tumors of the kidney or urinary bladder in rodents and some other substances: Methyl tert-butyl ether. In IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization.

and clearly described. The Panel differed on the extent of confidence in a CPN-based mechanism for the kidney effects. The Panel noted that the validity and applicability of the endpoints used for the derivation of the oral reference dose needs to be carefully examined, including the potential for CPN as a mechanism of action. The Panel also agreed that EPA should include details of all statistical analyses they conducted and a rationale for the final study selection and choice.

The meeting recessed at approximately 4:45 p.m. until the following morning.

Wednesday, August 16, 2017

Dr. Hill-Hammond reconvened the meeting at 9:00 am. She then turned the meeting over to Dr. Chambers.

Dr. Chambers invited Panel members to introduce themselves and provided a review of the agenda, highlighting the charge questions pending for discussion for the day. She also provided a brief recap of the questions discussed on the previous day. The Panel then continued with their discussion of the charge questions.

ETBE (cont'd.):

3d. Inhalation reference concentration for noncancer outcomes
The Panel reached consensus that, if the relevance of urothelial hyperplasia on the rat kidney to the human is accepted (see response to 3b), the derivation of the reference concentration is clearly described and scientifically supported. A Panel member suggested that sperm damage in the mouse model could also be considered as an appropriate endpoint. The Panel thought it would be valuable to assess route-specific potencies and cross-route evaluations by comparing estimated tissue doses of the metabolite tBA. Panel members commented that more careful statistical analyses may help elucidate sex differences and help in the decisions to include or exclude studies. The Panel agreed that EPA would need to strengthen their rationale for concluding that the ETBE effects on the rat kidney are relevant to the human kidney.

tBA:
3a. Noncancer kidney toxicity
The Panel agreed that the conclusions presented by EPA were clearly described however did not reach consensus about the robustness of the scientific support presented in the draft assessment. Just as with ETBE, the issue of CPN and its potential role and relevance to humans was also discussed methodically by the Panel.

The Panel agreed that EPA would need to provide more thorough explanation for consideration of CPN as a kidney effect relevant to human hazard assessment. EPA could consider other indicators besides suppurative inflammation and transitional epithelial hyperplasia as indicators of kidney effects or provide better justification for their choice.

3b. Noncancer toxicity at other sites

In general, the Panel thought that noncancer toxicity at sites, other than the kidney, should not be used as the basis for deriving an oral reference dose. One Panel member noted that additional toxicity studies are needed since the selected studies were older. For developmental toxicity, the Panel agreed that the EPA proposed classification of "inadequate evidence" should be changed to "minimal effects at otherwise toxic dose levels". The Panel also agreed that research on non-mammalian systems (e.g., zebrafish) to determine whether or not there are developmental targets of tBA should be pursued.

3c. Oral reference dose for noncancer outcomes

The Panel's discussion was premised on overall acceptance of the CPN resulting from exposure to tBA as being relevant to humans and therefore an appropriate endpoint (see response to 3a). There were divergent opinion regarding the relevance of this endpoint. The Panel agreed that when the endpoint was considered appropriate, the derivations by EPA were appropriate and clearly described but disagreed about the scientific support. The difference in consensus was based on the extent of confidence in a CPN and/or $\alpha_{2\mu}$-globulin based mechanisms for the observed effects.

The Panel agreed that the question of the validity and applicability of the endpoints analyzed for the oral reference dose needs to be carefully examined including the potential for CPN and/or $\alpha_{2\mu}$-globulin as mechanism(s) of effect. A few panel members also noted the EPA should include outcomes of statistical analyses they conducted and their rationale in study selection choice.

3d. Inhalation reference concentration for noncancer outcomes

The Panel agreed that, if the increases in the severity of nephropathy in the female rat is relevant to humans, the RfC derivation is clearly described and generally supported scientifically. The Panel had some reservations about the unconventional application of route to route extrapolation from an oral dose to an inhalation exposure. The Panel suggested that EPA should provide more details and justification for the application of the PBPK model. The Panel thought it would be valuable to assess route-specific potencies by a comparative evaluation of tissue doses of the metabolite tBA. The Panel also noted that EPA needs to strengthen their arguments for the relevance of tBA effects on the rat kidney to the human kidney.

4. Hazard Identification and Dose–Response Assessment: Cancer

ETBE:

4a. Cancer modes-of-action. Modes-of-action in the liver.

The Panel found the conclusion that liver tumors in male rats are relevant to human hazard identification to be scientifically supported. The Panel noted that evidence for lack of human relevance is stronger for the PPARα mode of action than CAR or PXR mode of actions. The Panel agreed that the report lacked clarity on specific information needed to conclude that a PPARα, CAR, or PXR mode of action is operative. Also there was some criticisms by the Panel of evidence regarding a potential PPARα, CAR, or PXR mode of action in that it appeared to be in error or inconsequential. The Panel noted that evidence for other [human relevant] modes of action were not clearly presented in the assessment. Although the charge question asks about

human relevance based upon mode of action, some Panel members expressed concern regarding the human relevance of the ETBE rat liver tumors because they were only observed at an excessively high dose (as defined in the EPA Cancer Guidelines[8]).

4b. Cancer characterization.
Some Panel members thought that "Inadequate Information to Assess" rather than "Suggestive Evidence of Carcinogenicity" was a more appropriate descriptor for ETBE, due to conflicting bioassay results, limited high-dose only benign tumors, non-genotoxicity, etc. Several Panel members thought that the descriptor "Suggestive Evidence" should be retained for all routes of exposure.

There was a divergence of opinions on the relevance and scientific validity of the initiation-promotion assay. Some Panel members thought the assay could forewarn of potential risks involving ETBE exposure. Some members pointed out the assay had been used as supportive evidence but that it was not appropriate to support a conclusion of carcinogenic potential. Other members thought the assay was not relevant to humans due to its design, thought it was not scientifically valid, and thought the assay had no value in risk assessment. The Panel agreed that EPA should devote more attention to assessing and describing the assays' design, interpretation limitations, relevance, etc.

4c. Cancer toxicity values.
The Panel agreed that EPA did not provide a rationale for performing a quantitative analysis for ETBE liver cancer. One Panel member provided a suggested rationale based on potential worker and consumer exposures. The majority of the Panel thought that performing a quantitative assessment of the data on ETBE liver carcinogenicity would not be useful for providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. However, several members of the Panel did favor conducting a quantitative analysis to provide some sense of the magnitude of potential risks. The Panel agreed that the Saito et al. (2013)[9] study was well-conducted and well-reported, but the majority of the members did not feel that the data for neoplastic liver lesions from inhalation exposure, by themselves, are a suitable basis for a quantitative analysis.

4d. Oral slope factor for cancer.
Most Panel members thought that the Saito et al. (2013) ETBE inhalation study was not suitable for developing an oral slope factor. Reasons included lack of biological relevance (excessive high dose, only one dose significantly increased). One Panel member thought the oral slope factor was scientifically supported. No alternative approach was suggested. No Panel comments indicated that the oral slope factor derivation was done incorrectly or was poorly described, some comments indicated the modeling was done correctly.

[8] U.S. EPA (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.
[9] Saito, A; Sasaki, T; Kasai, T; Katagiri, T; Nishizawa, T; Noguchi, T; Aiso, S; Nagano, K; Fukushima, S. 2013. Hepatotumorigenicity of ethyl tertiary-butyl ether with 2-year inhalation exposure in F344 rats. Arch Toxicol. 87: 905-914.

4e. Inhalation unit risk for cancer.

The Panel was unable to reach consensus. Some Panel members thought that the Saito et al. (2013) ETBE inhalation study was not suitable for developing an inhalation unit risk (IUR). Reasons included lack of biological relevance (excessive high dose, only one dose significantly increased tumor incidence).

Some Panel members thought Saito et al. (2013) was appropriate for dose-response analysis, indicating the IUR was scientifically supported. Some of those Panel members also had caveats regarding excessive high dose, only one dose significantly increased. No alternative approach was suggested. No Panel comments indicated that the inhalation unit risk derivation was done incorrectly or was poorly described; one comment indicated the modeling was done correctly.

tBA:

4a. Cancer modes-of-action. Cancer modes-of-action in the kidney (i) and thyroid (ii).

The Panel found the conclusion that male rat kidney tumors are relevant to human hazard identification to be scientifically supported. The draft assessment concludes that evidence for a mode of action involving $\alpha_{2\mu}$-globulin or CPN is incomplete or not coherent (respectively). While some tumors might be attributable to a $\alpha_{2\mu}$-globulin nephropathy augmented by CPN, others could be due to other unspecified processes. These processes are assumed to be relevant to humans. The Panel concurred with these conclusions. The Panel found the conclusion that thyroid follicular cell tumors in mice are relevant to humans to be scientifically supported. Some Panel members expressed concern whether an increase in thyroid follicular cell tumors was in fact demonstrated in male mice.

4b. Cancer characterization.

There was consensus that "Suggestive Evidence of Carcinogenic Potential" was the proper descriptor for tBA, as tBA caused renal tubule adenomas in male rats and follicular adenomas in female mice. The Panel agreed that this cancer descriptor is scientifically supported for oral exposure. No inhalation cancer bioassay data was found for tBA. The majority of the Panel agreed the renal tumors were attributable to $\alpha_{2\mu}$-globulin and CPN and thus were not relevant for human hazard evaluation.

If kidney tumors are not considered relevant, the cancer risk from exposure to tBA must be based on the thyroid tumors. The Panel agreed that EPA should clearly state the agency's policy that when a chemical is found to be carcinogenic by one route of exposure, it is assumed to be carcinogenic by other routes in the absence of evidence to the contrary.

4c. Cancer toxicity values.

The Panel found that the tBA assessment did not include a rationale for performing a quantitative analysis for tBA thyroid cancer. One Panel member provided a suggested rationale based on potential worker and consumer exposures. The Panel agreed that performing a quantitative assessment of the data on tBA thyroid carcinogenicity would not be useful for providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. Additionally, the Panel noted a concern for high uncertainty and potential for providing misleading risk estimates. However, several members of the Panel favored conducting a quantitative analysis to provide some sense of the magnitude of potential risks.

While the Panel agreed that the NTP (1995)[10] study was well-conducted and well-reported, the majority of the members did not feel that the data for neoplastic thyroid lesions from drinking water exposure, by themselves, are a suitable basis for a quantitative analysis because a single tumor was observed, and only at the highest concentration. With a statistically significant increase in tumors at the high dose only, and evidence from other studies supporting a potentially nonlinear mode of action, the NTP (1995) data are not sufficiently robust to provide a meaningful quantitative estimate of human cancer risk for tBA.

4d. Oral slope factor for cancer.
Most Panel members thought that the NTP (1995) tBA drinking water study was not suitable for developing an oral slope factor. One Panel member thought the oral slope factor was scientifically supported by the NTP (1995) data. No alternative approach was suggested by the Panel. No Panel comments indicated that the oral slope factor derivation was done incorrectly or was poorly described. Panel members commented that the modeling was done correctly.

4e. Inhalation unit risk for cancer.
Most Panel members agreed that the NTP (1995) tBA drinking water study was not suitable for developing an inhalation unit risk (IUR). One Panel member thought that a cross-route extrapolation could be done using default physiological parameters and appropriate absorption fractions. No alternative approach was suggested. No Panel comments indicated that the IUR derivation was done incorrectly or was poorly described. Some Panel members commented that the use of modeling to derive an inhalation unit risk for cancer was done correctly.

5. Susceptible Populations and Lifestages

ETBE:
The Panel agreed with EPA's conclusion that there is "plausible evidence" for a vulnerable subgroup, specifically individuals with the inactive form of ALDH2*2 variants, relevant to individuals in certain Asian subgroups. The Panel also agreed with EPA's determination of inconclusive evidence for CYP2A6 variants due to a lack of studies.

The Panel did have a couple of concerns, namely that the cited studies were from oral exposure routes only and no studies involved inhalation-based exposures. The assessment also did not mention the maternal-fetal unit as a possible susceptible population, which may be relevant due to changes in metabolism. The Panel agreed that sex specificity should also be noted, as this is a recurring observation throughout several of the sections and has potential relevance to susceptible populations.

tBA:
The Panel agreed with EPA's position that states "there is no identified susceptible population." The Panel did acknowledge that no human data were reported in the assessment; however,

[10] NTP (National Toxicology Program). 1995. Toxicology and carcinogenesis studies of t-butyl alcohol (CAS no 75-65-0) in F344/N rats and B6C3F1 mice (Drinking water studies) (pp. 1-305). (NTPTR436). Research Triangle Park, NC.

human data do exist to support altered metabolism with respect to xenobiotic metabolism during pregnancy for the maternal-fetal unit. The Panel concluded that this information should be cited in the assessment.

6. Question on the Executive Summary

ETBE:
The Panel stated that the Executive Summary as presented was clear and addressed the major conclusions of the draft assessment. The Panel noted that as revisions are proposed during the discussion, the Executive Summary will need to be changed accordingly. The Panel noted that, no matter how the questions of hazard and potency are resolved, the Executive Summary needs to capture the scientific pursuits that are vigorously exercised in the assessment, and specifically articulated for the broad audience. The Panel also agreed that the Executive Summary should acknowledge the degree of uncertainty stemming from the relative lack of significant dose response at low and intermediate doses, and that the conclusions drawn are critically dependent on best scientific judgments about the importance of observed toxicity endpoints and their relevance to health risks in humans.

tBA:
The Panel drew the same conclusions as stated for ETBE.

The meeting recessed at approximately 3:45 p.m. until the following morning.

Thursday, August 17, 2017

Dr. Hill-Hammond reconvened the meeting at 9:00 am. She acknowledged receipt of six requests for clarifying comments.

Clarifying Public Comments:

Dr. Cohen commented that CPN is a disease and is not relevant to humans. He also noted that a pathologist should have been included on the Panel per previous requests to the National Center for Environmental Assessment during the public review/comment periods for each assessment. Mr. Bromberg offered that EPA needed to raise the bar on their assessments to include a better scientific discussion. Dr. Nishimaki provided a comment that acetaldehyde does not induce tumors in rats. Dr. Banton commented on tBA and the proposed mode of actions. Dr. Bus commented on the available data sets for ETBE and tBA, noting that tumors only occur at dose saturation. Jason Fritz of EPA provided clarification with respect to EPA's cancer weight of evidence descriptions.

Writing Groups:
Following the clarifying public comments, the Panel broke out into writing groups to create a summary of the major points of consensus/dissension acknowledged during the meeting.
Report Out:
Dr. Chambers lead the discussion for the report out by identifying the charge question and assigned members. Each subgroup presented[xiii] points of consensus and points of dissension as it

related to their assigned charge question. Due to a limited amount of time, presentations concluded with question 4b.

Meeting Adjournment:
Dr. Chambers asked Dr. Hill-Hammond to review the next steps for the Panel. Dr. Hill-Hammond provided the following deadlines to the Panel.

- Due August 31 – revised individual comments
- Due August 31 – final comments on the report-out summary slide deck
- Due September 18 – draft report text

Finally, all meeting participants were thanked for their attendance and the meeting was adjourned at approximately 5:00 pm.

On Behalf of the Committee,
Respectfully Submitted,

/s/

Shaunta Hill-Hammond, Ph.D.
Designated Federal Officer

Certified as True,

/s/

Janice Chambers, Ph.D.
Chair, Chemical Assessment Advisory Committee Augmented for the ETBE/tBA Review

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.

Appendix A

List of Participants for the Chemical Assessment Advisory Committee (CAAC) Augmented for the Review of *ETBE and tBA* Public Meeting August 15 – 17, 2017

Name	Affiliation
James Bus	Exponent, Inc., on behalf of LyondellBasell
Shoji Fukushima	Japan Biology Research Center
Fukami Nishinaki	Japan Petroleum Energy Center (JPEC)
Samuel Cohen	University of Nebraska Medical Center
Janice Lee	US EPA
Marcy Banton	LyondellBasell
Kevin Bromberg	SBA Advocacy
Sylvia Carignan	Bloomberg BNA
Vincent Cogliano	US EPA
Katy Goyak	ExxonMobil
James Avery	US EPA
Jason Fritz	US EPA
Lou D'Amico	US EPA
Diana Wong	US EPA
Dahnish Shams	US EPA
Salina Tewolde	US EPA
Rachel Lehman	US EPA
Susan Rieth	US EPA
Ravi Subramaniam	US EPA
Tina Bahadori	US EPA
Mary Ross	US EPA
Samantha Jones	US EPA
Andrew Kraft	US EPA
Kris Thayer	US EPA

Requests for Call-In Information

Maria Hegstad	Inside EPA
Michael Dourson	University of Cincinnati
Christine Cai	US EPA
Jim Kim	OMB
Amanda Persad	US EPA
Hal White	US EPA
Vicki Soto	US EPA
David Reynolds	Inside EPA
Channa Keshava	US EPA
Summer Lingard-Smith	US GAO
Abby Li	Exponent
Lily Wang	US EPA
Roman Mezencev	US EPA
Bhaskar Gollapudi	Exponent

Materials Cited

The following meeting materials are available on the SAB webpage at: https://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/ad6dbaab343f7682852581540063b2a6!OpenDocument&Date=2017-08-15

[i] Agenda.
[ii] Federal Register Notice Announcing the Meeting.
[iii] Toxicological Review of Ethyl Tertiary Butyl Ether (External Review Draft - June 2017).
[iv] EPA presentation by Keith Salazar: Overview of the Draft IRIS Assessment of Ethyl Tertiary Butyl Ether (ETBE) August 15, 2017.
[v] Toxicological Review of tert-Butyl Alcohol (tert-Butanol) (External Review Draft - June 2017).
[vi] EPA presentation by Janice S. Lee: Overview of the Draft IRIS Assessment of tert-Butyl Alcohol (tert-Butanol) August 15, 2017.
[vii] List of Registered Public Speakers.
[viii] Ethyl Tertiary Butyl Ether (ETBE) Presentation by Fukumi Nishimaki, on behalf of Japan Petroleum Energy Center.
[ix] Ethyl Tertiary Butyl Ether (ETBE) Comments Submitted by Shoji Fukushima (Japan Bioassay Research Center) on behalf of Japan Petroleum Energy Center.
[x] Ethyl Tertiary Butyl Ether (ETBE) presentation submitted by Samuel M. Cohen.
[xi] tert- Butyl Alcohol (tBA) comments submitted by Samuel M. Cohen.
[xii] Charge for IRIS Assessment for Ethyl Tertiary Butyl Ether (ETBE), dated June 2017 and Charge for IRIS Assessment for tert-Butyl Alcohol (tert-butanol), dated June 2017.
[xiii] The CAAC-ETBE/tBA Draft Report Out Summary of Responses to Charge Questions.