Comments from Members of the Chartered SAB on the SAB Draft Report: 08-30-2018 Draft Review of EPA's Draft Toxicological Review of Ethyl Tertiary Butyl Ether and Draft Toxicological Review of tert-Butyl Alcohol Insert Title

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Comments from Lead Reviewers

Comments from Sue Marty

Please address the four quality review questions below from the vantage point of your own expertise:

1) Were the charge questions to the committee adequately addressed?

The SAB adequately addressed the charge questions. and provided detailed justification for the requested revisions. The three-tiered approach for recommendations provide a clear account of SAB's priorities when EPA revises these reports. In some cases, the SAB did not reach consensus on aspects of the Toxicological Reviews for ETBE and tBA, which may complicate EPA's revisions to these reports. The SAB made some distinct recommendations for improving the reports, which included:

- The addition dermal studies and contact dermatitis (tBA) as well as non-mammalian studies should be included in the evaluation.
- Clarification of the PBPK modeling text to improve understanding and transparency and consideration of a human parameterized model.
- Evaluation of dose metrics for ETBE and its metabolites (acetaldehyde and tBA) to provide information about proximate toxicant(s) and mechanisms of toxicity.
- Additional text on why chronic progressive nephropathy (CPN) is relevant to humans. In a Tier 2 recommendation, the SAB suggests a workshop on the human relevance of kidney effects in rats with CPN – a good idea!
- The SAB recognized "plausible evidence" that there could be a sensitive subpopulation (and vulnerable life stages) for ETBE based on human polymorphisms in ALDH2. Male reproductive toxicity in the presence of ALDH2 mutations may serve as a sensitive endpoint for noncancer RfC for ETBE.
- EPA's route-to-route extrapolation for tBA from oral doses that affect kidney to inhalation doses that affect kidney are not supported by the data.
- The MOA for ETBE liver tumors is undetermined and therefore, must be considered relevant to humans. More information is needed on carcinogenic MOAs. As part of this description, the EPA should references case studies or provide information on the types of data needed to verify these MOAs.
- There was no consensus in the SAB about the relevance to humans of male rat kidney tumors by tBA; thus thyroid tumors are a better basis for the cancer risk assessment.

In addition, the SAB provided important feedback on EPA's systematic review (a critical element for public acceptance of these reports) and the need to reorganize the report text in order to better integrate toxicity outcomes with PBPK modeling as well as link data tables more clearly to the text. The SAB's proposed revisions will strengthen the report.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Overall, the draft report was very well done. Below are some proposed changes from Tier 2 to Tier 1 recommendations that the SAB may wish to consider:

- Given some of the data limitations (e.g., timing of histological data), the SAB suggestion on p. 21 to use the newer IARC criteria for alpha-2μ-globulin is supported and could be moved to Tier 1.
- The requirement to provide more justification for human relevance of CPN (or exacerbation of CPN) is a Tier 1 recommendation for ETBE (p. 21), but a Tier 2 recommendation for tBA (p. 23). Consider making this Tier 1 for both substances. This is critical as the endpoints used for noncancer risk assessment would change if kidney is not adequately supported as the most sensitive target organ.
- Given that ALDH2 mutations may pose a risk for sensitive human subpopulations, then the Tier 2 recommendation on p. 25 (i.e., calculating an RfC for male reproductive effects of ETBE) should become Tier 1 recommendation.
- On p. 28, one Tier 2 recommendation notes that some ETBE tables within the EPA report need units for completeness and interpretability. This is a Tier 1 recommendation for tBA (same page) and should be a Tier 1 recommendation for ETBE.
- On. p. 34 (tBA), the recommendation that EPA should provide statistical analysis should be moved to Tier 1. This is standard practice.
- On p. 38, EPA should explain that the assignment of cancer classifications are an EPA Cancer Guideline policy-based decision. This is an easy addition and provide important context for the reports.
- On p. 39, EPA should expand its discussion on potential MOAs for thyroid tumors and potential tBA site of action, particularly if this is the focus of the cancer risk assessment

Typos/clarifications to consider:
p. 18 l. 10 "There is no "consistent dose-response relationship" for this <u>dose metric dose</u> (page B-27),…"
p. 24, l. 15-16 "Minor effects (skeletal variations, postnatal deaths at a specific time point) were only observed…" Postnatal deaths do not fit in a parenthetical behind "minor effects".
p. 2, l. 2 in the letter to the EPA Administrator: "…it is critical that further justification be provided by EPA f."

3) Is the draft report clear and logical?

Yes, the draft report is both clear and logical. The tiered recommendations make it easy for the EPA to identify priorities that need to be addressed before the reports are finalized. The report is redundant in some places as many of the same issues apply to both ETBE and tBA; however, this may be due to the EPA's need to revise two separate reports. Thus, the SAB has documented report recommendations separately for each compound to facilitate report revisions.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Generally, the conclusions and recommendations are adequately supported by the body of the report. In a few cases, additional consideration or support by the SAB may be warranted; specifically:

- The SAB advocates that the LOAEL for lethargy and ataxia should be considered in the reference dose analysis (p. 27) in the context of reproductive and developmental toxicity (Tier 3 recommendation). However, the rationale for this recommendation is not well described in the preceding text. More discussion on

this point, and the relevance to the reference dose, may be beneficial for the EPA. Also, if this occurs at high dose levels, is this a greater concern for neurotoxicity than reprotoxicity (as neurotoxicity will likely occur first)?

- Does the EPA have a guidance on the use of liver hypertrophy as an endpoint for establishing a reference dose? On p. 28 (ETBE) and p. 29 (tBA), the SAB recommends that liver hypertrophy serve as the basis for the oral RfD if urothelial hyperplasia is not selected; however, liver hypertrophy is often an adaptive response. If a specific magnitude of change is needed, please reference relevant supporting guidance (e.g., OECD) for designating liver hypertrophy as adverse.
- On p. 30 (Tier 2 recommendation on p. 31), the SAB recommends that increased absolute kidney weight in ETBE-treated male rats provides a more sensitive index of kidney toxicity than urothelial hyperplasia and thus, would provide a more health protective RfC value. This may not set a good precedence as kidney weight is a non-specific endpoint that can be modulated by other factors, including body weight. As the SAB notes, kidney weights were correlated with histopathological changes in the kidneys, then it might be better to link the RfC with adverse kidney histopathology, not kidney weights (even though the difference in RfCs is not excessively large with kidney weights). Increased severity of nephropathy is associated with structural and functional changes in the kidney, not weight.

5) Does the Letter to the Administrator adequately reflect the findings of the SAB report?
The conclusions of the SAB review committee are clearly and consistently expressed in the Letter to the Administrator. The letter is well constructed and includes the primary findings and rationale for the SAB's key findings. The letter also highlights areas of consensus and disagreement during the SAB's deliberations.

Comments from Dr. Kristina Mena

Were the charge questions to the committee adequately addressed?

Yes, the charge questions to the committee were adequately addressed. Specifically, the different tier levels were applied and provide useful feedback for the EPA.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

The draft report addresses each section of EPA's document comprehensively by considering both EPA's approaches and conclusions. What is particularly helpful is the range of expertise on the SAB of those who contributed to the draft report, including their knowledge and familiarity with the peer-reviewed literature. Because of this range in expertise, however, there is some inconsistency within the SAB regarding agreement of some of EPA's methods and results. While it is important to convey to the EPA the lack of consensus within the SAB on specific issues, it may lead to confusion by the EPA when interpreting this draft report if SAB recommendations are not explicitly stated with supporting reasons explaining why those specific recommendations were made.

3.1. <u>Literature Search/Study Selection and Evaluation – Systematic Review Methods</u>

The literature search is of utmost importance and the SAB did a thorough job of addressing related key issues. Any recommendations below stem from ensuring the EPA receives specific guidance from the SAB to remedy any EPA inconsistencies and uncertainties the SAB noted.

Under 3.1.1. ETBE, page 8, lines 10-12 Regarding the statement that the SAB agrees with the overall strategy for the literature searches "with a few exceptions", are all of the exceptions specified in this section? In line 24, could additional databases be recommended? What other keywords should be included, or is it more important to simply know why EPA chose to not use all possible synonyms?

Page 8, lines 28-36, Does EPA's development of IRIS-specific guidelines address the SAB's concern that the ETBE hazard assessment is limited due to the nature of the continuing literature search process? Can the SAB provide specific guidance?

Page 9, lines 4-13 These are important comments that are critical to the EPA report. Perhaps consider including these recommendations under Tier 1.

Under 3.1.2. tBA, page 10, lines 32-33 Are there recommendations for other databases to use, and under what parameters?

Page 11, lines 1-5 I agree that clarification for additional, manual searches among review articles (yet inconsistent) are warranted here. Yet, how should the EPA interpret this comment since it did not reach SAB consensus? Is this comment related to one of the Tier 1 recommendations on page 12 (third bullet)? (However, this and the other bulleted recommendations do not mention review articles.)

Page 12, lines 21-23 I suggest considering moving this Tier 2 recommendation to Tier 1.

3.2 <u>Hazard Identification – Chemical Properties and Toxicokinetics</u>

3.2.3. Choice of dose metric.

Under 3.2.3.1. ETBE, page 18, line 29 Would it be appropriate or helpful for the SAB to expand on the statement "Concentration of parent ETBE may be a relevant dose metric."?

3.3. <u>Hazard Identification and Dose-Response Assessment: Noncancer</u>

3.3.1. Noncancer kidney toxicity.

Under 3.3.1.1. ETBE, The differences in opinions of SAB members about toxicity and relevance to humans are well described. The related Tier 1 recommendation is appropriate. However, would it be possible for the SAB to reach a consensus – and add a statement – about the importance of a conservative approach in protecting human health? Or, would this not accurately reflect the opinions and discussions of the SAB? Such a statement would support this Tier 1 recommendation.

Under 3.3.1.2. tBA, page 23, lines 15-16 What is different about this recommendation related

to human health relevance from the recommendation in 3.3.1.1. ETBE that places it in Tier 2?

Would it be beneficial for the EPA to add information that supports and justifies their approach and conclusions? Would this help the SAB reach a consensus to better understand EPA's assessment? Would the SAB support EPA's assessment if clarification was included so that the reader understood EPA's interpretation?

3.4. <u>Hazard Identification and Dose-Response Assessment: Cancer</u>

3.4.1. Cancer modes-of-action in the liver.

Under 3.4.1.1. ETBE, page 35, lines 33-35 Does the statement presented here about the human relevance of the male ETBE rat liver tumors refer to the comments on page 34, lines 30-48? The statement seems out of place.

3.5. <u>Question on Susceptible Populations and Lifestages</u>

Under 3.5.1. ETBE, pages 46-47, lines 45-48 and 1-3 Besides pregnant women and fetuses, does the SAB think other lifestages should be addressed or mentioned (even to state lack of supporting evidence)?

3) Is the draft report clear and logical?

Cover letter to Administrator Wheeler, first page, lines 39-40 The statement, " . . . the SAB is unable to reach consensus with respect to how the Agency interpreted the ETBE database . . . " perhaps should be reworded to be more specific regarding EPA's assessment and subsequent conclusions. Also, there is a typographical error in line 2 of the second page of the cover letter.

Executive Summary, page 2, line 11 – awkward wording [" . . . whether fits to data . . ."]

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Overall, the recommendations are supported by the content of the draft report; however, the lack of SAB consensus in several places may make it difficult for the EPA to properly interpret and appropriately address recommendations. This may not be an issue since the SAB recommendations do tend to favor EPA's stance on a topic with the SAB's request focusing on EPA strengthening and justifying their approach. However, this leads to the question: Since there was a lack of consensus, how did the SAB choose the particular recommendations and why? Was it to indeed take a conservative approach (as mentioned above in this quality review), or was it to align with EPA's current report and ask EPA to justify their conclusions (rather than recommend something in opposition)?

In some places of the draft report, as noted earlier in this quality review, the SAB identified and explained recommendations critical to the assessments of ETBA and tBA but the recommendations were placed in Tier 2 rather than Tier 1 (such as Tier 2 recommendations on page 10 and page 12). In these cases, there appears to be an inconsistency between SAB recommendations and supporting information or justification.

Comments from Dr. Ken Portier

Overall a well-written, clear and concise report. There is some text duplication but this is required to address separately the questions for Ethyl Tertiary Butyl Ether (ETBE) and tert-Butyl Alcohol **(**tBA).

1) Were the charge questions to the committee adequately addressed?

Charge Question 1. Literature search/study selection and evaluation – systematic review methods.

Both ETBE and tBA responses are clear and concise.

It is hoped that as EPA continues to apply and strictly adhere to the IRIS-specific guidelines for literature reviews to these assessments, the kinds of comments found in this section, particularly comments relating to the lack of reasoning behind deposition of individual research studies, will decrease.

Charge Question 2. Hazard ID - Chemical properties, toxicokinetic modeling, and choice of dose metric.

Both ETBE and tBA responses are clear and concise.

It is clear the Panel had difficulty linking toxicity/cancer outcomes with the modeling efforts because of the layout of the assessment document. For this charge question, the discussion of dose metrics is fairly short. A more comprehensive discussion can be found in charge question 3 and 4. While some of the material from charge questions 3 and 4 might be relocated to better answer the choice of dose metric component of charge question 2, nothing would be gained by such a move and the flow of the hazard argument would be disrupted. I recommend leaving it as is.

Charge Question 3. Noncancer kidney toxicity, toxicity at other sites, oral reference dose and inhalation reference concentration.

Both ETBE and tBA responses are clear and concise. Recommendations seem reasonable based on discussion in the text.

Page 27: The first Tier 1 recommendation has to do with including contact dermatitis in the hazard identification. This recommendation seems to come “out of the blue” since there is no discussion of the dermal route of exposure preceding this recommendation. Similarly, the last Tier 3 recommendation related to research on non-mammalian systems has no accompanying discussion. A little discussion/justification of these recommendations is needed.

Page 28: The last Tier 1 recommendation relates to a more integrated presentation and could use an example of how the current text makes tracking information difficult. Same for the fourth bullet of Tier 3 recommendations on page 29.

Page 32: Not clear to me why lack of a report on statistical analysis of individual studies (indicated on line 9 as a critical omission) is not considered for a Tier 1 recommendation but is in Tier 2.

Charge Question 4. Cancer MOAs, characterization, toxicity values, oral slope factor, and inhalation unit risk.

Page 37: The discussion on cancer MOAs in the kidney for tBA is very short and no recommendations are provided. Incompleteness of data supporting the proposed MOA is mentioned. Why not recommend that EPA request or develop data to further clarify this MOA?

Page 37: The discussion on a cancer MOA in the thyroid based on observed thyroid follicular cell tumors in rodents is two lines and no recommendations are provided. Elaborate on "there is uncertainty as to whether an increase in thyroid follicular cell tumors is demonstrated in male mice."? Some elaboration is provided on page 39 in the tBA cancer characterization but even this is minimal. Why aren't the Tier 2 and Tier 3 recommendations on page 40 (tBA Cancer Characterization) more pertinent in this section?

Charge Question 5. Susceptible populations and lifestages.

After seeing very tightly worded recommendations in previous sections, the Tier 1 recommendations on page 48 seem very long. Most of the recommendation text could be moved to the discussion and only the last line, the true recommendation, left as the bullet text.

Charge Question 6. Quality of executive summary.

Text is clear and concise.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Inconsistences in formatting of the references were noted specifically parentheses around publication dates and occasionally an extra parenthesis.

3) Is the draft report clear and logical?

Yes.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, in most cases with the exceptions noted above.

Comments from other SAB Members

Comments from Dr. Deborah Hall Bennett

1) Where charge questions addressed?

   Although there was disagreement on several questions among committee members, all of the questions appeared to be addressed.

   Question 3.2.1.1: The committee obviously spent a lot of time checking original references for this section. It would be easier for the EPA to fix the errors if inconsistences found by the committee were provided in an appendix.

2) Are there any technical errors?

3) Is the report clear and logical?

   The report is slightly confusing given the extent of disagreement among panel members, but in the body of the report, they have done their best to provide a clear report. However, there are several sections in the executive summary where there is a lack of clarity given the complexity of the issues. Two specific examples are given below, but the whole section should be carefully gone over to ensure clarity, particularly for a non-toxicologist.

   In the section of the conclusion discussing non-cancer hazard identification, the paragraph should begin with a brief statement noting the decision the EPA, as it is confusing to jump into the disagreement among the SAB members without knowing what was done.

   For the non-toxicologist readers, it would be helpful to state in the cancer hazard identification section of the conclusion that 2µ-globulin is not a relevant pathway for human exposure.

4) Are conclusions supported by body of report?
   Please see comment above about providing additional clarity to this section. One specific comment is that I thought the conclusion dwelled too much on the one aspect they did not evaluate on the literature given that the body of the report was largely favorable on this aspect. Further, I thought too much weight was given to the arguments against the EPA conducting an analysis in the summary, and not enough weight to the idea that the EPAs other option was to strengthen the description of why they made the choices they did.

Comments from Dr. Alison C. Cullen

1. Were the charge questions adequately addressed?
   The charge questions were all addressed and many completely resolved. However, there were several instances where the SAB review panel did not reach consensus on the science underlying health effects pertinent to charge questions. For example, with respect to noncancer kidney effects, SAB did not reach consensus regarding how the Agency interpreted the ETBE database, nor whether noncancer kidney effects in rats should be

considered relevant to humans. In addition, for tBA SAB did not reach a consensus on oral reference dose for noncancer kidney outcomes. Another lack of consensus emerged on the panel regarding EPA's calculation of an inhalation unit risk for ETBE, and in particular again regarding whether the data were suitable for developing an IUR due to a potential lack of biological relevance.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?
   I am not aware of technical errors in the report or omissions.

3. Is the draft report clear and logical?
   The draft report is clear, logical, and very well organized.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
   Yes.

Comments from Dr. Otto Doering

- The charge questions were adequately addressed
- I did not find technical errors or omissions in the report or issues that were not adequately dealt with in the draft report
- I found the draft report clear and logical. The report was very well organized. The format of charge, discussion and recommendations was very helpful. The tiered recommendations served to set priorities. The point/counterpoint discussions were appropriate and very useful.
- The conclusions drawn or recommendations provided were supported by the body of the draft report.

Comments from Dr. Susan Felter

The Draft SAB report on EPA's assessments for ETBE and TBA are challenging because the EPA assessments are problematic and the SAB subcommittee could not reach an agreement on several points. I spent quite a bit of time going back to the original data (and specifically the cancer bioassays) on ETBE because of the clear lack of consensus and questions raised in this report. My written comments submitted today are focused on the cancer risk assessment for ETBE only; I will share additional comments on the noncancer assessments and for TBA prior to our meeting.

1. Were the charge questions to the committee adequately addressed?

Please see Q#2 below, as my response is relevant to both Q#1 and Q#2.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

My comments that follow are limited to the cancer risk assessment for ETBE, which I found highly problematical, both for the hazard identification, and the dose-response.

Hazard Identification (cancer classification): The SAB draft report states that "there is scientific support for the EPA's conclusion that liver tumors in male rats are relevant to human hazard identification" and that the cancer descriptor of "Suggestive Evidence of Carcinogenic Potential" for ETBE is appropriate (p. 4, ll 2-3). I disagree with this and it's not clear that the draft report supports this. There are multiple bioassays for ETBE, with only one inhalation study showing an increase of one tumor type in one sex at a whopping high dose. All other studies were negative, and ETBE is not a genotoxic chemical.

- The inhalation bioassay (Saito et al. 2013) showed no increase in any tumors in female rats; an increase was seen in male rats only for liver tumors (almost all benign) at the *highest dose only*. This dose was 20,900 mg/m^3, which is a whopping high exposure. It is noted that the final body weight in the male rats were 94%, 94%, and 75% of controls for the low-, mid-, and high dose groups, suggesting that the high dose exceeded the Maximum Tolerated Dose (MTD). Saito et al. equated their high dose to an intake of 4222 mg/kg/day, which is much higher than the limit dose for an oral bioassay (and over 4-times higher than the highest doses tested in oral bioassays). The finding of an increase in benign liver tumors at only the highest dose which is associated with a 25% decrease in body weight should not lead to the classification of this substance as a possible carcinogen, and certainly should not be the basis for a quantitative evaluation involving linear low-dose extrapolation. As a side note -- there were several tumor types with a *decreased* incidence at the high dose (in particular, fibromas of the subcutis in males and mammary gland fibroadenomas in the females).

Saito et al. (2013); JPEC (2010b) rat, Fischer 344 inhalation – vapor male (50/group): 0, 500, 1,500, 5,000 ppm (0, 2,090, 6,270, 20,900 mg/m^3)[b]; female (50/group): 0, 500, 1,500, 5,000 ppm (0, 2,090, 6,270, 20,900 mg/m^3)[b] dynamic whole body inhalation; 6 hr/d, 5 d/wk for 104 wk; generation method, analytical concentration, and method reported	Incidence Male Dose (mg/m^3)	Adenoma	Carcinoma	Adenoma or carcinoma
	0	0/50	0/50	0/50
	2,090	2/50	0/50	2/50
	6,270	1/50	0/50	1/50
	20,900	9/50*	1/50	10/50*
	Female Dose (mg/m^3)	Adenoma	Carcinoma	Adenoma or carcinoma
	0	1/50	0/50	1/50
	2,090	0/50	0/50	0/50
	6,270	1/50	0/50	1/50
	20,900	1/50	0/50	1/50

- In the oral bioassay by Suzuki et al. (2012), there were 4/50 male rats in the *control* group with liver tumors (2 adenomas and 2 carcinomas) but *none* in any of the treated groups. The highest dose was 542 mg/kg/day. For perspective, the authors of the inhalation bioassay (Saito et al., 2013) equated their high dose (5000 ppm) to an intake of 4222 mg/kg/day (see earlier comment about this being a whopping high dose). In females, there was 1 adenoma in

the high dose only.

Suzuki et al. (2012); JPEC (2010a) rat, Fischer 344 oral – water male (50/group): 0, 625, 2,500, 10,000 ppm (0, 28, 121, 542 mg/kg-d)[a]; female (50/group): 0, 625, 2,500, 10,000 ppm (0, 46, 171, 560 mg/kg-d)[a] daily for 104 wk	Incidence Male Dose (mg/kg-d)	Adenoma	Carcinoma	Adenoma or carcinoma
	0	2/50	2/50	4/50
	28	0/50	0/50	0/50
	121	0/50	0/50	0/50
	542	0/50	0/50	0/50
	Female Dose (mg/kg-d)	Adenoma	Carcinoma	Adenoma or carcinoma
	0	0/50	0/50	0/50
	46	0/50	0/50	0/50
	171	0/50	0/50	0/50
	560	1/50	0/50	1/50

Likewise, in another oral (gavage) bioassay by Maltoni et al. (1999), there were *no* liver tumors in male or female rats at either 250 or 1000 mg/kg/day (with relatively large dose groups of 60 rats/sex/dose):

Maltoni et al. (1999) rat, Sprague-Dawley oral – gavage male (60/group): 0, 250, 1,000 mg/kg-d; female (60/group): 0, 250, 1,000 mg/kg-d 4 d/wk for 104 wk; observed until natural death NOTE: Tumor data not reanalyzed by Malarkey and Bucher (2011).	Incidence Male Dose (mg/kg-d)	Liver neoplasm	Female Dose (mg/kg-d)	Liver neoplasm
	0	0/60	0	0/60
	250	0/60	250	0/60
	1,000	0/60	1,000	0/60

Even in the bioassay that involved pre-treatment with a genotoxic carcinogen (DMBDD; Hagiwara et al., 2011) showed no increase in liver tumors in rats at the low dose and no tumors even at 1000 mg/kg/d in rats that did not receive the DMBDD initiation:

Liver Neoplasm		
Hagiwara et al. (2011); JPEC (2008d) rat, Fischer 344 oral – gavage male (30/group): 0, 300, 1,000 mg/kg-d daily for 23 wk following a 4-wk tumor initiation by DMBDD[c] [†] no DMBDD initiation	Incidence Male	
	Dose (mg/kg-d)	Liver neoplasm
	0	1/30
	300	1/30
	1,000	6/30*
	0[†]	0/12
	1,000[†]	0/12

Regarding the quantitative cancer assessments -- the draft report states that there is no rationale provided by EPA to perform a quantitative analysis (for either ETBE or TBA) and notes that "it is unlikely that performing a quantitative assessment of the potential carcinogenicity data would be instructive…" I would argue that the quantitative analysis conducted by EPA is highly inappropriate. Of course, if one concludes that there is no cancer hazard, then one would not do a quantitative assessment. But even if the EPA maintains it conclusion that there is "suggestive evidence of carcinogenic potential," to conduct linear extrapolation based on an increased tumor incidence seen at only the highest dose of one bioassay (with all others being negative) is problematic. It is worth noting the conclusion of the authors of the bioassay used by EPA to calculate the slope factor state:
"Whether the hepatotumorigenicity of ETBE observed in the present study can be extrapolated to humans is inconclusive at present since ETBE has no genotoxicity. There is a threshold in carcinogenic potential of non-genotoxic carcinogen, and the no-observed-effect level (NOEL) for hepatotumorigenicity of ETBE is considered as 1,500 ppm in rats. Since induction of tumor is hepatocellular adenoma (benign tumor) at high dose, male only, low incidence and proliferative lesion at high dose, the reference value for general population for tumorigenic effect of ETBE by inhalation exposure is calculated as 15 ppm (an uncertainly factor supposed to be in the order of 100 times)."

While I have not completed my review of TBA, I note the statement in the draft report that, "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." It's not clear why the subcommittee took this position on TBA, but not for ETBE.

In addition to the inappropriate calculation of an inhalation slope factor, the EPA used the inhalation bioassay to derive an oral slope factor even though the drinking water and gavage bioassays are *entirely negative*. This is highly inappropriate. It is challenged in the draft SAB report (from pdf p. 53):
Since the Saito et al. (2013) ETBE inhalation study is not suitable for developing an oral cancer slope factor, EPA should not derive an oral slope factor by route extrapolation absent pharmacokinetic/pharmacodynamic modeling that demonstrates consistency between the oral

and inhalation study results.
But it is not adequately challenged in the executive summary, and does not raise questions about the importance of the negative oral bioassays

3. Is the draft report clear and logical?

I found it difficult to follow the draft report and where/whether it agreed with the EPA or not. This could reflect decisions being made in isolation versus consideration of the data/assessment as a whole. For example, in the cover letter (2nd page, ll 40-41), the report states, "The SAB agrees that the methodology applied for deriving the oral slope factor chosen by the EPA is scientifically supported for both ETBE and tBA. No consensus, however, was reached regarding the EPA's calculation of inhalation unit risk (IUR) for ETBE. Some members conclude that the data are not suitable for developing an IUR due to a potential lack of biological relevance for ETBE." This does not make sense since the oral slope factor for ETBE was based on the *same data* as the inhalation IUR for ETBE. It also seems contradicted by
I also note that the draft report states (p 2, ll 19-20) that "route-to-route extrapolation should not be conducted until an alternate metric is identified…" Given that EPA used route-to-route extrapolation to calculate the oral slope factor, this sentence is inconsistent with the earlier statement that the SAB agrees that the methodology applied for deriving the oral slope factor is scientifically supported for ETBE.

Regarding noncancer effects, the draft report states that the SAB did not reach a consensus on whether the noncancer kidney effects for ETBE should be considered a hazard relevant to humans (p. 2, ll 27-28) but at the bottom of the same page states that noncancer toxicity at sites other than the kidney "are less suitable" because they occurred at much higher exposure levels. It's not clear what this means for those members of the SAB who felt that the kidney effects were not relevant to human health.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

See comments above.

Comments from Dr. John Graham

I have reviewed the Executive Summary (ES) of the draft SAB report for logic and clarity of argument. Overall, I thought the draft ES was well done, especially given that there appears to be a lack of SAB consensus on some key issues. My only reservation is that the draft ES does not advance a scientific strategy -- short run or long run -- for resolving the points of disagreement within the Committee. When such a powerful group of experts is brought together, one might hope that they could devise a knowledge-generation strategy to resolve the candid disagreements that they have expressed.

I have only a few specific reactions and editing suggestions. First, on p. 1 lines 31-32, I recommend that the phrase "with a few exceptions" be moved to appear after the word "are". Second, p. 2, lines 27-28, please consider this more concise wording: "The SAB is unable to reach consensus about whether the EPA properly interpreted the ETBE database for

noncancer kidney effects." The same edit applies to lines 36-37. Third, on p. 2, line 38, please insert "in dosed rodents" after "noncancer kidney effects". Fourth, you might insert on p. 3, lines 33-34, the phrase "pursuant to EPA guidelines," after "are assumed", Fifth, p. 4, line 17, I recommend deleting the word "Additionally" because the entire paragraph appears to be an explanation as to why the Committee believes that supplying a quantitative assessment would not be informative. Finally, on p. 5, lines 15-16, I would remove the word "should" because it is not necessary given prior use of the word recommends in the same sentence.

Comments from Dr. Anne Smith

Were the charge questions adequately addressed?

There are a number of issues where the review committee notes a lack of consensus. In most cases, the recommendations that follow provide a constructive response to the charge questions that reflect the uncertainties leading to the lack of committee consensus. However, this does not occur in Section 3.4.5.1 regarding calculation of an IUR for inhalation cancer risk from ETBE. Although formally the review responds to that specific charge question, as precisely worded, I feel that more effort could be given to providing a constructive response on how EPA might better address that area of scientific uncertainty too.

2. **Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report**? None that I have identified.

3. **Is the draft report clear and logical?** Yes.

4. **Are the conclusions drawn or recommendations provided supported by the body of the draft report?** Yes. However, in some cases no recommendation is provided at all. As I commented above, some form of recommendation would be useful to add to section 3.4.5.1, if only that EPA's assessment more thoroughly discuss the sources of scientific uncertainties reflected in the committee's lack of consensus.