NOTICE: **Do Not Cite or Quote.** The following draft report comments are for review and to assist meeting deliberations by the CAAC-ETBE/tBA committee. These comments do not reflect consensus advice or recommendations, and have not been reviewed or approved by the chartered SAB and do not represent EPA policy.

Comments for review by the SAB Chemical Assessment Advisory Committee augmented for the review of ETBE and tBA (SAB CAAC-ETBE/tBA Committee)

This document provides a summary of comments submitted for the 3/22/18 and 3/27/18 teleconferences and correspond to only those charge questions listed for discussion during the 6/6/18 teleconference[1]. The following comments from committee members and EPA were submitted in response to the draft report available at https://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/46495425F4649F7E85258227003EC276?OpenDocument.

6/5/18

[1] 6/6/18 Teleconference Agenda. Available at https://yosemite.epa.gov/sab/sabproduct.nsf//MeetingCalBOARD/DCBC685C251C4F488525827200604327?OpenDocument

Charge Question	Report Section	Comment by	Comment	Proposed revisions (if provided)
4c - ETBE	3.4.3.1	Budroe	The use of the words "highly unlikely" are inappropriate, since no discussion of the magnitude of any potential uncertainty took place during the CAAC meeting. Also, the draft Report states with regard to both ETBE and tBA that "several members favor conducting a quantitative analysis to provide some sense of the magnitude of potential risks." (page 41, lines 31 – 32 and page 43, lines 12 – 13). This does not support the use of the "highly unlikely" descriptor. *This comment also applies to page 4, lines 7 – 10 and 23 – 24, page 41, line 11 and page 42, line 40.* The Report states "The SAB concludes it is highly unlikely that performing a quantitative assessment of the data on ETBE liver carcinogenicity would be useful for "providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities", and "Any quantitative analysis based on this limited evidence would be highly uncertain and potentially misleading.", but also states "The SAB agrees that the Saito et al. (2013) study is well-conducted and well-Reported", and "several members favored conducting a quantitative analysis to provide some sense of the magnitude of potential risks." The Report also makes a Tier 1 recommendation that "EPA should refrain from conducting a quantitative analysis for ETBE carcinogenicity or [bolding added] explain the limitations of the analysis and clearly state the intended purpose is to simply provide some sense of the magnitude of potential risks." This section of the Report ignores the SAB-reviewed 2005 Guidelines for Carcinogen Risk Assessment policy, and makes a Tier I recommendation that would allow EPA to perform a dose-response assessment if the results of that analysis are qualified as to its limitations. This introduces ambiguity as to the impact of this Report section on Section 3.4.5.1. Additionally, the statement that "Any quantitative analysis based on this limited evidence	

			would be highly uncertain and potentially misleading" goes beyond the discussion of this charge. Finally, the discussion of modeling the Saito *et al.* liver tumor data set was inaccurate – all ETBE concentrations induced increased tumor incidences compared to controls. The data points which did not reach statistical significance still provide useful information for dose-response modeling purposes. Unfortunately, the ETBE/tBA Expanded CAAC did not include any biostatisticians that could have provided appropriate expertise to the discussion of this issue. In light of this information, the Tier III recommendation is unjustified.	
4c - tBA	3.4.3.2	Budroe	The Report does not state that the NTP (1995) tBA drinking water study was not well-conducted and reported. In fact, that study was very well conducted and reported, and because of the positive tumor results in two species/sex, would justify a "Likely to be Carcinogenic to Humans" designator. Therefore, the comments for Section 3.4.3.1 also apply to this Report section - this section of the Report ignores the SAB-reviewed 2005 Guidelines for Carcinogen Risk Assessment policy described above, and makes a Tier I recommendation that would allow EPA to perform a dose-response assessment if the results of that analysis are qualified as to its limitations. This introduces ambiguity as to the impact of this Report section on Section 3.4.4.2. Additionally, the statement that "The SAB deems it highly unlikely that performing a quantitative assessment of the data on tBA thyroid carcinogenicity would be useful for "providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities." goes beyond the discussion of this charge question at the CAAC meeting, ignores the lack of consensus on this issue and is therefore unjustified. Finally, as with the Section 3.4.3.1 discussion on modeling, the discussion of modeling the NTP 1995 drinking water study female mouse thyroid tumor data set was inaccurate – one other tBA concentration induced increased tumor incidences compared to controls. The data points which did not reach statistical significance still provide useful information for dose-response	

			modeling purposes. Unfortunately, the ETBE/tBA Expanded CAAC did not include any biostatisticians that could have provided appropriate expertise to the discussion of this issue. In light of this information, the Tier III recommendation is unjustified.	
4d	3.4.4	*GENERAL points*		
		Roberts	Our opinion that the oral slope factors for ETBE and tBA are scientifically sound seems in contradiction to a recommendation that they not be developed.	
		Rhomberg	The report notes doubt from the Panel about the sufficiency of available studies for use in quantitative cancer risk estimates, yet it also says "The SAB concludes that the oral slope factor chosen is scientifically supported for both ETBE and tBA" at p.44, line 31 and for tBA at p.45, line 34.	
			I agree with the concerns about the oral slope factors that the report expresses. The SAB's report discusses at some length these concerns about the ability to create meaningful and useful oral slope factors for both ETBE and tBA. It is therefore incongruous for the report then to simply say a few lines beyond such discussions that the oral slope factors are "scientifically supported" without addressing these concerns. Perhaps the document's references to the oral slope factor being scientifically supported (at the places cited in the first paragraph, above) can be changed to… "the oral slope factor chosen is developed in accord with standard EPA principles, but its scientific support must be tempered in view of the concerns the SAB has expressed above regarding the suitability of the bioassay data for quantitative analysis and the meaningfulness and utility of risk calculations based on them."	
4d -ETBE	3.4.4.1	Budroe	Lines 6 through 23 of Report page 44 appear to state that consensus was reached for the issue of the suitability of the Saito et al. (2013) study for developing an oral cancer slope factor. Lines 31 through 36 of page 44 indicate that no consensus was reached, especially for bullets 2 and 3 of lines 6 through 23. Those bullets should be struck, as should lines 25 through 29, where again, no consensus was reached on this suggested policy change.	A suggested rewrite for section 3.4.4.1 is listed below: The Saito et al. (2013) study used three concentrations of ETBE and observed significant increases in liver tumors in male but not female rats at the highest inhaled concentration only. The oral cancer slope factor was obtained by converting the inhalation point of departure to an oral

				dose using rate of ETBE metabolism in the liver, which was derived from a PBPK model. The SAB is concerned that the Saito et al. (2013) ETBE inhalation study is not suitable for developing an oral cancer slope factor, due to the issues associated with developing an oral cancer slope factor using the Saito et al. (2013) study described below: • Unlike the Saito et al. (2013) ETBE inhalation study, well-conducted contemporary oral cancer studies up to the limits of solubility did not demonstrate cancer. The route differences could be due to pharmacokinetic or toxicodynamic processes, but either would require quantification to demonstrate cross-route consistency of the tumor observations. • As EPA's analyses indicated, combining oral and inhalation studies did not result in a consistent dose response relationship using the dose metric of average daily rate of ETBE metabolism at periodicity. This argues against route extrapolation using this dose metric; no other dose metric was identified that provided consistent results between oral and inhalation exposures. The SAB has no alternative approach suggestion for developing an oral cancer slope factor, and noted that the oral slope factor derivation was well described. The SAB also agrees that the modeling was performed in accord with standard EPA principles. ***The following recommendations are noted:***

				Tier 1: EPA should not derive an oral ETBE slope factor by route extrapolation from the Saito et al. (2013) ETBE inhalation study absent pharmacokinetic/pharmacodynamics modeling that demonstrates consistency between the oral and inhalation study results.
		Rhomberg	Add more support for the following. P.44, lines 6-29 – "The SAB is concerned that the Saito et al. (2013) ETBE inhalation study is not suitable for developing an oral cancer slope factor … "	
		Benson	P. 44, L31-36. The comments made in this paragraph seem to conflict with those in the paragraphs above. See info starting on line 6 of this page.	
		Barton	I do not think the oral cancer slope factor for ETBE developed using route extrapolation is scientifically supported or justified. No oral slope factor could be developed based upon the negative results of the oral cancer bioassay in rats. This negative well conducted study is inadequately noted in the SAB report when discussing the oral slope factor derived by route extrapolation. As noted in the report and the EPA's Toxicological Review for ETBE, the dose metric used for the route extrapolation does not provide a consistent dose-response relationship between the oral and inhalation studies. The BMD (in mg/kg/day) for the inhalation study reported in Table 2.7 for the Toxicological Review for ETBE is actually slightly below the highest dose in the oral study that was negative for male rats and found only 1/50 adenomas in the female rats. This reflects the lack of consistent dose-response relationship between the two studies using the chosen dose metric. Therefore, EPA is developing an oral slope factor despite a well conducted negative oral rat carcinogenicity study with a dose-metric that doesn't provide consistency between the routes; this does not make scientific sense. Text throughout the report needs to reflect this lack of scientific support.	
4d - tBA	3.4.4.2	Budroe	1) The draft Report states "The SAB agrees that the NTP (1995) tBA drinking water study was not suitable for developing an oral cancer slope factor. The SAB was concerned about the lack of biological relevance due to the magnitude of the high dose and	**The following section rewrite is suggested:** The NTP (1995) tBA drinking water study used three doses of tBA and observed significant increases in thyroid follicular

			the possibility of nonlinear metabolism kinetics at that dose." (page 45, lines 17 – 19) This paragraph tries to infer that a consensus was reached on this issue. However, the draft Report also states (page 45, lines 36 – 43): "Some members conclude the EPA's choice for oral slope factor for tBA was scientifically supported. Reasons supporting this position include: • The lack of supporting data for a mouse anti-thyroid MOA, indicating that there is no reason to conclude that the female mouse thyroid follicular cell tumor data are not relevant to human cancer risk assessment. • The tBA dose producing female mouse thyroid follicular cell tumors in the 1995 NTP study did not cause excessive treatment-related mortality or otherwise exceed the Maximum Tolerated Dose (MTD) in females although increased mortality is present in males at this dose. • EPA policy permits the dose-response modeling of tumor data where only the high study dose induces a significant tumor increase." It seems fairly obvious that the members that concluded the EPA's choice for oral slope factor for tBA was scientifically supported also believe that the NTP (1995) tBA drinking water study was suitable for developing an oral cancer slope factor. The draft Report needs to be revised to indicate the lack of consensus on this issue. 2) The draft Report states "The SAB is not comfortable with EPA's policy to permit the dose-response modeling of tumor data where only the high study dose induces a significant tumor increase. In the case of the tBA-induced female mouse thyroid follicular cell tumors, the SAB observed that having only one significantly elevated dose and two doses with response statistically indistinguishable from the control response provides little useful information in the range of interest for BMD/BMDL calculation (i.e., between the single significantly elevated dose and the control response).	cell tumors in female mice at the high dose and non-significant increases at the low dose. The dose-metric for the dose-response analysis used to develop the oral cancer slope factor was exposed dose. The SAB was not able to reach consensus on the suitability of the NTP (1995) tBA drinking water study for developing an oral cancer slope factor. Some members were concerned about the potential lack of biological relevance due to the magnitude of the high dose and the possibility of nonlinear metabolism kinetics at that dose. However, some members conclude the EPA's choice for oral slope factor for tBA was scientifically supported. Reasons supporting this position include: • The lack of supporting data for a mouse anti-thyroid MOA, indicating that there is no reason to conclude that the female mouse thyroid follicular cell tumor data are not relevant to human cancer risk assessment. • The tBA dose producing female mouse thyroid follicular cell tumors in the 1995 NTP study did not cause excessive treatment-related mortality or otherwise exceed the Maximum Tolerated Dose (MTD) in females although increased mortality is present in males at this dose. This indicates the tBA high dose was not excessive. •The issue of high dose non-linear metabolism kinetics was speculative, as there is no mouse tBA TK model available. The SAB has no recommendations to alternative approaches for developing an oral cancer slope factor and there are no

			The SAB also suggests that EPA may want to rethink their policy to use the Multi Stage Cancer model as the preferred cancer dose-response model. The SAB noted that many different models could fit these data with equally good statistics of fit, but with widely different dose-response functions in the dose range of interest. Therefore, EPA should consider a wider choice of models when performing cancer dose-response analyses." (page 45, lines 21 – 32) The draft Report should note that carcinogen doses producing tumor incidences not significantly different than controls can still contribute to a cancer dose-response analysis. In the case of tBA-induced female mouse thyroid follicular cell tumors, NTP noted a significant positive trend for dose-response, indicating that tumor data set is suitable for quantitative dose-response analysis. That information should also be included in the draft Report. Additionally, the review of the draft Toxicological Reviews of ETBE and tBA was not intended to be a forum for a revisitation of EPA cancer dose-response policy (contained in the 2005 Guidelines for Carcinogen Risk Assessment, which was reviewed by the SAB) on either 1) dose-response modeling of tumor data where only the high study dose induces a significant tumor increase or, 2) the preferred use of the Multistage Cancer model for cancer dose-response analysis. If that was the intent of the review, it would have been expected that the augmented CAAC would have included biostatisticians familiar with these issues – it did not.	comments to indicate that the oral slope factor derivation is poorly described or was not performed in accord with standard EPA principles. The following recommendations are noted: Tier 1: No recommendation due to lack of SAB consensus.
		Rhomberg	I don't have specific language to suggest, but I think these statements just cited need to be modified to temper the support in view of the questions raised P.45, lines 17-32 – "The SAB agrees that the NTP (1995) tBA drinking water study was not suitable for developing an oral cancer slope factor … "	
		Benson	P. 39, L 44: In absence of data, would say that the evidence for cancer following tBA inhalation is <u>inadequate.</u>	

		Rhomberg	Add more support for the following. P.45, lines 17-32 – "The SAB agrees that the NTP (1995) tBA drinking water study was not suitable for developing an oral cancer slope factor … ".	
4e - ETBE	3.4.5.1		No written comments provided by the panel.	
4e - tBA	3.4.5.2	Budroe	As stated in the comment on section 3.4.4.2, the high dose of tBA in the NTP 1995 drinking water study did not exceed the MTD. There is therefore no reason to conclude that dose was excessive. Additionally, the issue of high dose non-linear metabolism kinetics is speculative, as there is no mouse TK model available. These issues were raised in the comments following the meeting discussion, indicating a lack of consensus for these issues.	**The following section rewrite is suggested:** EPA decided to not develop an inhalation unit risk for tBA from the mouse thyroid tumor data because of the lack of a mouse toxicokinetic model, and from the male rat kidney tumor data because of the inability to determine the relative contribution of α2u-globulin nephropathy to tumor formation. The SAB concurs with EPA's decision. Some members raised additional concerns about the study, including the lack of biological relevance due to the magnitude of the high dose, and the possibility of nonlinear metabolism kinetics at that dose. Other members believed that 1) the high dose of tBA in the NTP 1995 drinking water study did not exceed the MTD, and thus there is no reason to conclude that dose was excessive, and 2) the issue of high dose non-linear metabolism kinetics was speculative, as there is no mouse tBA TK model available. ***The following recommendations are noted:*** **Tier 1**: The SAB supports EPA's decision to not present an inhalation unit risk for tBA.
5 -ETBE	3.5.1	Morandi	P48, L32: The SAB includes the "following review". We need to provide the citation.	
5 - tBA	3.5.2	Lash	Page 49, lines 20-23 (PDF p. 59): Although the specific CYP enzyme responsible for tBA metabolism has not been directly	

			demonstrated, it is likely that CYP2E1 is the primary CYP for tBA metabolism. This is based on the known, albeit somewhat broad, substrate specificities of the various CYPs. Genetic polymorphisms in CYP2E1 as well as developmental and sex-dependent differences in its expression are quite well known, which can inform about potential vulnerable populations.	
6 -ETBE	3.6.1		No written comments provided by the panel.	
6 -tBA	3.6.2		No written comments provided by the panel.	
Letter to Administrator		Barton	The SAB is encouraging or recommending that EPA create a human inhalation parameterization for the PBPK model. As this is a Tier 2 suggestion, I do not think it should be included in the letter to the administrator and those lines should be deleted.	
		Budroe	P2, lines 28 – 33: "The SAB finds no rationale provided for the EPA's decision to perform a quantitative analysis of carcinogenic potential for either ETBE or tBA. The SAB noted that it is highly unlikely that performing a quantitative assessment of the potential carcinogenic data would be useful for providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities for either ETBE or tBA." The use of the words "highly unlikely" are inappropriate, since no discussion of the magnitude of any potential uncertainty took place during the CAAC meeting. Also, the draft Report states with regard to both ETBE and tBA that "several members favor conducting a quantitative analysis to provide some sense of the magnitude of potential risks." (page 41, lines 31 – 32 and page 43, lines 12 – 13). This does not support the use of the "highly unlikely" descriptor. This comment also applies to page 4, lines 7 – 10 and 23 – 24, page 41, line 11 and page 42, line 40.	
		Stern	P 2, line 29 and ff. is contradictory to lines 35 and ff. The first statement is generic and would appear to be negative with respect to both inhalation and oral slope factors for both ETBE and tBA, while the second, is not clearly negative for either route or chemical.	

Executive Summary		Barton	The SAB is encouraging or recommending that EPA create a human inhalation parameterization for the PBPK model. The language in the executive summary should be changed to "encouraging" as the current text makes it sound as if it was a Tier 1 recommendation.	
		Stern	P. 4, line 34 - The statement, "The SAB concludes that the oral slope factor chosen is scientifically supported for both ETBE and tBA," is immediately proceeded by strong statements that the SAB does not believe that it is appropriate to derive cancer potency estimates for either ETBE or tBA given the nature of the dose-response data. Possibly, the summary statement on line 34 refers to the actual calculation of the cancer slope factor rather than the appropriateness of the slope factor. However, the text does not make this clear.	
		Rhomberg	I don't have specific language to suggest, but I think these statements just cited need to be modified to temper the support in view of the questions raised • P.4, line 6 -- "The SAB notes that no rationale is provided … for the decision to perform a quantitative analysis in the case of ETBE." • P.4, line 12 – "there is considerable concern about the ability of dose-response modeling to provide meaningful and useful information" • P.4, line 24 – "Similarly, there does not appear to be a rationale for performing quantitative analysis for tBA and it is highly unlikely that performing a quantitative assessment of the data on tBA thyroid carcinogenicity would be useful…" • P4. The report notes doubt from the Panel about the sufficiency of available studies for use in quantitative cancer risk estimates, yet it also says "The SAB concludes that the oral slope factor chosen is scientifically supported for both ETBE and tBA" at p.45, line 34.	
		Lash	P5, lines 36-38 (PDF p. 15): I do not like the second clause of this sentence. I think the point could be made differently. For example, it can state: "...and that the default conclusion should not be that an endpoint is relevant to human risk when there is uncertainty about such relevance. Rather, a more accurate conclusion is that relevance to humans cannot be ruled out."	

		EPA	Draft report language ETBE, page 2 lines 18-19: “The SAB finds the choice of the rate of metabolism of ETBE to be a reasonable dose metric; however, it is not recommended for extrapolation from inhalation to oral routes of administration of ETBE.” Clarification EPA is seeking clarification on whether the panel is suggesting that metabolic rate could be used for animal-human extrapolation within a route of exposure, and that choice of an alternate metric is based on the assumption that the alternate metric provides a more consistent dose-response evaluation.	
		EPA	Draft report language tert-Butanol, page 2 lines 44-45: In the Executive Summary, the SAB CAAC concludes that “The SAB agrees that noncancer toxicity at sites other than the kidney should not be used as the basis for deriving an oral reference dose (RfD) for tBA.” Clarification EPA is seeking clarification on how this advice can be interpreted with regards to the repeated tier 1 recommendation above that “the LOAEL for lethargy and ataxia should be considered in the reference dose analysis.”	