Quality Review of "SAB review of *Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE) (2017)* and *Toxicological Review of tert-Butyl Alcohol (2017).*

1. Were the charge questions adequately addressed?

The charge questions appear to be well addressed. In cases where the Panel could not reach consensus in responding to the question EPA posed, different views by Panel members are described and subsequently explained. This seems to provide an appropriate strategy to capture the breadth of expertise and divergent positions of Panel members. Issues of disagreement between Panel members also provide a logical focus of final report revisions to better strengthen the technical basis of EPA's final conclusions regarding the human health hazards of ETBE and tBA.

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

Pg 9 Line 24-26

The Panel states that:

"The SAB is not able to provide advice on whether the EPA's evaluation of study methods and quality are applied objectively because of the lack of documentation within the draft assessment. There is no clear documentation on the comparative quality evaluation for each of the studies."

The transparent evaluation of study methods and quality provides the foundation for the analyses and conclusions drawn in these assessment. As a result, it seems inappropriate that clearly documenting this information for key individual studies in the final reports (perhaps as a supplement) is regarded as a Tier 2 rather than Tier 1 recommendation (Page 10, lines 2-4). Thus, it is suggested to move this recommendation to Tier 1.

This comment also applies to tBA (Pg 12, lines 20-23).

Pg 23 Line 11

For section 3.3.1.2 No Tier 1 recommendation is provided. However, should not the Tier I recommendation provided for ETBE (page 21, line 33-35) apply here?

Pg 36 Line 38-39

The text references a suggested workshop in Section 3.3.1.1. However, there does not appear to be mention of a workshop in this section. Please clarify/revise for consistency.

3. Is the draft report clear and logical?

The report is well and logically written. A few minor editorial concerns / clarification are identified below.

Pg Line 6

Typo .. Integrated

Pg 14 Line 44

Please clarify what is meant by “average daily concentration of tBA at periodicity”

Pg 15 Line 14-16

Sentence awkward/unclear, please reword.

Page 25 Line 33 fix typo

Pg 28

The last Tier 2 recommendation for ETBE (lines 10-12) is considered as two separate Tier 1 recommendations for tBA (Line 48; Pg 29 Line 1). Further, the Tier 2 recommendation for ETBE (Lines 15-20) is presented as two Tier 2 recommendations for tBA. Suggest making the Tiers/text consistent.

Pg 32 Line 22

Delete “mostly”

Pg 38 Line 16

Fix Typo

Pg 40 Line 17

It is stated that there is supporting evidence that ETBE is genotoxic. However, in an earlier section (Pg 37 Line 39) it is stated there a lack of evidence that ETBE is genotoxic. Please clarify this apparent inconsistency.

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

Pg 6 Line 36

Suggest revising to clarify why the panel is supportive …e.g.

“The SAB supports this initiative since applying such guidelines in the future will improve consistency in maximizing the use of existing information in substance hazard assessments”

Pg 19, Lines 7-9; 30-33

The Panel suggests that text describing toxicity/cancer outcomes be located nearer to modeling analyses. I question if this recommendation can be strengthened by instead encouraging EPA to better integrate this information into the report rather than simply changing location of where such information is presented.

Pg 30 Line 23

Suggest revising “a more health-protective RfD value” to “a lower, more conservative RfD value” given the divergent opinions expressed regarding whether the effect upon which this RfD is based has relevance to humans.

Pg 30 Lines 38-40

These sentences appear contradictory. Suggest revising to better clarify intent, .e.g.

“The Agency should reconsider and further justify utilizing the exacerbation of CPN in female rats as the toxic endpoint for RfC derivation.”

Pg 34 Line 4

Based on discussion Pg 32 lines 45-48 it would appear that an important Tier I recommendation not stated is that “EPA provides a description of the rationale used for adopting a route to route extrapolation for derivation of the oral RfC”

This recommendation logically compliments the Panel’s current Tier I recommendation that requests EPA provide more detailed information regarding the specific application of the PBTK model used.

Pg 35 Line 11-13

The Panel states:

“As a result, the MOA analysis for receptor-mediated events appears more subjective than it should. Further, some of the EPA criticisms of data regarding key events are seen as inconsequential or in error, which further detracted from this section.”

The second sentence is vague and will be difficult for EPA to address. The report should better explain which EPA criticisms are viewed by the Panel as inconsequential and erroneous.

Pg 35 Line 33-35

The Panel raises concern about the human relevance of ETBE rat tumors based upon data limitations beyond MOA considerations and implies that this concern needs to be better addressed in assessing human relevance. However, this concern is not reflected in the subsequent recommendations at the end of this section. It would seem appropriate to state the need for EPA address this concern as an additional recommendation.

Pg 36 Lines 1-4

The Panel states:

“Acetaldehyde is proposed as a strong candidate MOA for male rat liver tumors, but the plausibility of this MOA is not well explored. Evidence for this MOA should be developed and presented more thoroughly; or, alternatively, the Agency is encouraged to reduce emphasis on this MOA in the final assessment.

The Panel suggests two possible alternatives for addressing acetaldehyde as a potential MOA for male rat liver tumors. The first option (conduct and present further analysis e.g. comparisons with acetaldehyde tumor data as stated on Pg 35 Lines 29-30) seems logical to determine if available data supports or refutes this hypothesis. This effort would strengthen the technical basis of the cancer hazard assessment and associated position on relevance for humans. However, I question the rationale for the alternative recommendation to reduce emphasis on this MOA in the final assessment. This path would seem to weaken the technical basis of EPAs evaluation which seems counter to the intent of the charge question response.