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**Compilation of the SAB Chemical Assessment Advisory Committee augmented for the review of ETBE and tBA (SAB CAAC-ETBE/tBA Committee)
Member Preliminary Comments on the ETBE/tBA Draft Report**

The following comments from committee members were submitted in response to the draft report available at <https://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/46495425F4649F7E85258227003EC276?OpenDocument>. This compilation contains all comments received as of March 8, 2018.

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Dr. Lorenz Rhomberg

My only comments at this juncture are that 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” (p.4, line 34). A similar statement appears for ETBE at p.44, line 31 and for tBA at p.45, line 34.

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 at the following places:

- 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...”
- 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 ... “
- 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 ... “

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.”

Dr. Alan Hoberman

I have reviewed the draft ETBE/tBA report. Overall I have no major changes to recommend as I think the reproductive and developmental toxicity endpoints have been adequately evaluated based on the data available.

Tier 3 recommendations for future work in special populations and additional work with current state of the art methodologies is also warranted as noted in the report.

For consistency the discussions of reproductive toxicity for ETBE are discussed in separate sections for males and females (pages 24 and 25); but for tBA only a single section on reproductive toxicity (page 27) is presented.

I agree that at least some mention of the conclusions (positive and negative) for developmental and reproductive toxicity should be noted in the executive summary.

Dr. Alan Stern

In the letter to the Administrator, on pg. 2, line 29 and ff. the following statement occurs:
“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.”

However on lines 35 and ff., the following statement occurs:

“The SAB agrees that the oral slope factor chosen by the agency is scientifically supported for both ETBE and tBA. No consensus, however, was reached regarding the EPA’s calculation of inhalation unit risk for ETBE.”

These two statements seem mutually contradictory on their face. 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:

pg. 4, line 34 - The statement, *“The SAB concludes that the oral slope factor chosen is scientifically supported for both ETBE and tBA,”* is immediately preceded 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.

Literature Search:

pg. 8, line 15 and ff. - The statement, *“Of note, the strategy for the literature search for the draft ETBE assessment did not follow all the recommendations as outlined by the NRC (2011), except for some aspects of the selection of the studies to be included in evidence tables,”* seems gratuitous as adherence to the NRC recommendations was not part of the charge question and further, it is not clear what schedule the EPA had committed to with regard to the adoption of the NRC recommendations at the time of the writing of this document. **I strongly suggest deleting this statement and all other comparisons to NRC recommendations.**

lines 30-41 - This appears redundant with the above wording, and as above the comparison of the

pg. 10, lines 1-3 - As above I don’t believe that reference to the NRC recommendations is relevant to our charge here.

pg. 25-31 - Notwithstanding that the wording here indicates consistency with NRC recommendations, this comparison is again, inappropriate.

pg. 11, lines 28-30 - As above, delete consideration of consistency with NRC recommendations.

pg. 12, lines 8-14 - As above regarding NRC.

Non-cancer kidney toxicity

pg. 21, line 14 - Add “that” – “And that fact *that* they happen...”

Inhalation Reference Concentration – Tier 2 Recommendations

pg. 32, lines 21-23 - Endpoints such as DNA breaks, and 8-oxo-deoxyguanine have rarely, if ever been used as the basis for RfD/RfC derivation. This is probably because they’re significance in downstream toxicity (e.g., tumor development) is not clear in any given case. Furthermore, “minor histopathological changes” are difficult to characterize in the abstract with respect to their relevance for RfD/RfC development. As a rule of thumb such changes tend to be considered if they can be demonstrated to be on a pathway of progression to more clearly adverse effects, but not if such a pathway cannot be, at least reasonably, conjectured. I suggest deleting these recommendations.

Cancer Characterization

pg. 38, line 35 - I don’t believe that inclusion of “lack of genotoxicity” in the list of weaknesses in the evidence consistent with the designation “suggestive evidence of carcinogenicity” is appropriate. While (positive) evidence of genotoxicity can strengthen evidence for potential carcinogenicity to humans, the absence of evidence of genotoxicity should not be considered as evidence against such a designation. This is because there are cancer MOA that do not proceed through genotoxicity. I suggest deleting these words.

Dr. Harvey Clewell

Overall, I agree with the report. I have a few comments/corrections:

Cover letter:

p. 2, line 19: “...finds that...” should be “...agrees with...”

p. 2, line 35: “The SAB agrees that the oral slope factor...” should be “The SAB agrees that **the methodology applied to derive** the oral slope factor...”

Report:

p..3, line 4: replace "if urothelial hyperplasia in male rats (Suzuki et al., 2012) is used for hazard 4 assessment," with "if EPA’s assertion is accepted about the human relevance of the increased urothelial 16 hyperplasia in the male rat kidneys (Saito et al, 2013),”

p. 3, line 5: “then the derivation” should be “then **the methodology applied in** the derivation”

p. 3, line 11: “then the derivation” should be “then **the methodology applied in** the derivation”

p. 4, line 34: “The SAB concludes that the oral slope factor...” should be “The SAB concludes that **the methodology applied to derive** the oral slope factor...”

p.4, line 36: “...of inhalation...” should be “...of **an** inhalation...”

p.5, lines 3-5: Either delete the last sentence or add: “However, this approach is not consistent with the best available science.”

Dr. Isaac Pessah

In summary:

-Throughout the document: To follow the formal and widely used notation for this protein the alpha_{2u}-globulin with alpha in Greek symbol but u not in Greek symbol. Also, choose either to not subscript 2u (preferable) or subscript neither.

See links at: <https://www.ncbi.nlm.nih.gov/protein/?term=alpha2u+globulin>

Consider correcting throughout the document.

- Page 26 lines 43-44: indicate routes of exposure; oral on line 43 and inhalation on line 44
- Page 31 line 10: include ppm conversion for 21,000 mg/m³ in parentheses for completeness.
- Page 31 line 12: indicate exact strain of mouse. C57B6C3F1? Other?
- Page 32 line 23: indicate exact strain of mouse. C57B6C3F1? Other?
- Page 41 line 25: benchmark dose lower confidence limit has already been defined above; use BMDL

Dr. Lawrence Lash

1. Page 5, 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."
2. Page 24, lines 44-46 (PDF p. 34): One cannot say a parameter is increased but there was no statistically significant difference; if no statistically significant difference, then there is no change. Period!
3. 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.
4. Grammar note: The document frequently uses the word "since" inappropriately when words such as "because" or "inasmuch as" or "as" are more appropriate. "Since" should only be used when making reference to a time-dependent process.
5. There are a few sections in which no recommendations have been made yet the subsections listing Tier 1, 2, and 3 recommendations are still present. If it is intended that recommendations should be added, then this is fine as place holders. If there are no recommendations to be added, however, then these subsections should be deleted or replaced by a statement that the SAB had no specific recommendations for these sections.

Dr. Maria Morandi

In general, the Draft Report reflects the responses to the Charge Questions and the Panel's discussions. In particular, most areas where the Panel did not reach consensus together with the rationales supporting differing opinions are provided clearly.

The main issue to discuss in the upcoming meeting is the apparent contradiction between the Panel's judgments that quantitative analysis for ETBE and tBa carcinogenicity is not scientifically supported because of a lack of rationale and insufficient robustness of the available data, and the judgment that the oral slope factor for ETBE is scientifically supported. As I recall, this apparent contradiction reflects dissent within the Panel, but this is not stated clearly.

A second issue that should be discussed is the lack of any specific recommendations to EPA in the several cancer assessment areas including cancer MOAs in the kidney and thyroid for tBa. The Panel should consider if there is any advice we could provide to the Agency.

Below is a list of housekeeping corrections to the report (including suggested editorial changes).

General

1. The reference list does not include most of the citations in the text of the report. They can be obtained from the Toxicological Reviews.
2. The list of abbreviations includes many that are not used in the Draft Report, and does not list others [e.g., (CVL (concentration in venous blood), Km (Michaelis constant), AUC (area under the curve), Cmax (maximum plasma levels)]. CL is listed as confidence limit but it is used for designating concentration in liver in the report.

Specific

Letter to the administrator:

First page

line 15: remove the comma in "...assessments, entitled..."

line 44: remove "...consideration of..."

Second page

lines 12-13: rephrase sentence to: "Regarding noncancer kidney outcomes from exposure to ETBE, the SAB did not reach consensus on an oral reference dose."

Executive Summary and Responses to Charge Questions:

Page 1

line 17: replace ";" by "," in "...effects; and..."

line 33: "...the EPA's ETBE and tBA Toxicological Review (U.S EPA 2017a, b, c, d) documents."

Page 2

line 10: "...SAB recommended that an ETBE and tBA..."

line 28: "Although ~~consideration of~~ the role..."

Page 3

line 32: "...the conclusion, that male rat..."

line 33: "...the conclusion, that male rat..."

line 37: "...by CPN, and are, therefore, not relevant..."

line 45: "...in EPA's 2015 Cancer Guidelines (U. S. EPA, 2005)."

Page 4

line 24: "...for tBA. ~~and i~~ It is highly unlikely..."

line 36: move the sentence starting in line 36 as the first sentence of the next paragraph which starts in line 39.

Page 5

line 23: "This difference ~~is~~ in body weight gain..."

lines 36-37: The second part of this sentence, i.e., "...and simply not being certain about the irrelevance of an endpoint to human risk does not result in certainty of relevance." is not clear.

Page 9

line 2: "...and international agencies) ~~were~~ limited."

line 17: "...individual issues ~~with~~in specific studies."

Page 11

line 12: "...only IPCS (1987 ~~a,b~~) and OSHA (1992) are included

Page 12

line 8: "...or from ~~the~~ Literature Search Strategy/Study..."

Page 14

line 42: "...U.S. EPA (2017) document "PK/PBPK Model Evaluation for 42 the IRIS Assessments of Ethyl Tertiary Butyl Ether and tert-Butyl Alcohol"

Page 15

line 2: "...the assessment ~~had~~ ~~have~~ been identified..."

Page 19

line 3: "...by the ~~a~~Agency."

line 4: clarify the sentence "The SAB notes that where EPA's analysis question; is ETBE in blood versus in liver?"

Page 21

line 37: "...section 1.3.1 on page 1-1098, lines 29-32..."

Page 32

line 13: " ~~is not and~~ should be clearly stated within the..."

line 32: "...which, if responsible,..."

Page 33

line 11: "...assessment ~~does not and~~ should provide..."

line 33: "...(page 2-12, lines 12-14...)..."

Page 34

line 1: "...RfCs derived..."

Page 38

line 33: "... (adenomas (+1 carcinoma) ...) ..."

Page 48

line 25: "...have susceptibility to health effects from ETBE exposure."

lines 32-33: "The SAB includes the following review...": the review is not cited.

Page 49

line 2: "...report ~~is~~ does not fully utilize ~~ing~~ available..."

line 22: "...of tBA, it is unknown..."

line 35: "...difference is in body weight..."

Dr. Hugh Barton

I have two major concerns.

First, the letter to the administrator (p1 lines 31-33) and the executive summary (p2 lines 9-11) contain language indicating the SAB is encouraging or recommending that EPA create an 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. 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.

Second, 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.

Dr. Janet Benson

Page	Lines	Comments
1	18-20	Last sentence in this paragraph repeats the info in the first. Delete?

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2	31 -33	Are more detailed criteria published more recently than IARC 1999? What about all the material presented by the public in the September meeting? Could serum biomarkers for kidney lesions be identified by SAB for evaluation (BUN?).
3	14 - 21	Who is it that accepts EPA's assertions about human relevance of rat nephropathy produced by ETBE and tBA? Could this be included in the paragraph?
4	40	Later in the document I did not find discussion of male thyroid follicular cell tumors.... just notation that B6C3F1 females developed them in the NTP study.
4	14	Specify these tumors are in liver and only for one sex.
7	10	Please clarify what (eg, EPA "need" means).
8 - 9	44 (page 8) to 2 (page 9)	This section is a bit confusing.... basically, primary sources in reviews and government documents were not reviewed to determine quality/accuracy?
14	41	Access to the modeling software <i>and ability/knowledge of how to use.</i>
15	24	Later in document the relevance of acetaldehyde is questioned...maybe say something about that here.
22	13-15	Maybe a combination of endpoints should be considered as a whole. Can serum endpoints be suggested for evaluation.... BUN...creatinine?
22	31	End sentence after "humans". "was also discussed methodically" was stated in the above line. Is redundant.
23	9	Is there any evidence that an increase in kidney weight in rodents relates to an adverse event in a human? Is it the chemical exposure that provides evidence for such a relationship? Is this secondary to edema or inflammation, hyperplasia? What is the biological relevance? The same question arises in other sections of this document. If there is (or isn't), it might be useful to state.
25	24-33	I very much agree with the Tier 1 statements for ETBE and TBA (page 27, lines 21 -31).
29	31	Might be helpful to state why liver hypertrophy should be used as an alternative to nephropathy.
31	1-2	I have the same concern about the relevance of increased kidney weight for setting reference concentration/dose. Especially when underlying pathology is not identified.
31	38	Approximately 4 times higher than the selected RfC (<i>based on what parameter?</i>).
32	20-33	Suggest these Tier 2's be Tier 1's.
33	6 - 12	Totally agree with comments in this paragraph.
35	37 - 45	Very much agree with the content of this paragraph.
36	20-21	For line 22, should add that tumors were only observed in one sex as well. If one sex makes thyroid tumors suspect (female but not male mice, then the same should be true for liver tumors especially at extremely high dose levels.

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36	30 - 42	Suggest moving Tier 2 comments to Tier 1.
37	24-31	No recommendations?
37	40-42	Maybe this section could be beefed up a bit to say that thyroid tumors were seen in female but not male mice... (was there a dose response in females?). Was there a question in the literature/final report about the presence of tumors in males? The info in this section is a bit cryptic.
38	3 - 10	Again, no recommendations?
39	44	In absence of data, would say that the evidence for cancer following tBA inhalation is <u>inadequate</u>
44	31-36	The comments made in this paragraph seem to conflict with those in the paragraphs above. See info starting online 6 of this page.

Dr. Stephen Roberts

General Comments:

This draft is adequate as a first compilation, but requires significant polishing to improve readability.

There are many inconsistencies in our discussion and recommendations. The panel split on the human relevance of the noncancer kidney effects for both ETBE and tBA is not adequately or consistently treated in the report, and our comments on the cancer dose-response assessment are also confusing.

Specific Comments:

1. Pg. 21, lines 21-31 – Public commenters play an important role in bringing information to the attention of the panel, but the report should focus on the opinions of the panel. There was a major split of the panel regarding interpretation of the kidney findings that affects many of the charge questions. The basis for this difference of opinions merits additional discussion in my opinion. As the report now stands, the preceding paragraph lays out the EPA rationale for concluding that kidney effects of ETBE are relevant to humans, and this paragraph merely states that some members agreed and others didn't. Nowhere is the basis for the difference of opinion explained. This panel split affects many of the responses to charge questions, and some additional discussion is needed I think.

2. Pg. 21, lines 37-45 – My recollection from the meeting was that some panel members noted that urothelial hyperplasia occurred with CPN and that its human relevance was therefore questionable. That view is not reflected in this paragraph.

3. In some places, the split opinion is acknowledged but appears to be minimized. For example, on pg. 21, lines 19-23, the report states “The overall conclusion that kidney effects are a potential human health hazard associated with tBA exposure is appropriate and scientifically supported. However, the SAB notes that some members concluded that all the tBA noncancer kidney effects ... are, therefore not scientifically supported nor relevant for hazard assessment in humans.”

4. In other places, it is not mentioned or acceptance of noncancer kidney effects is implicit. For example, on pg. 31, lines 16-18, our report states: “Also of note, the Agency should consider utilizing the exacerbation of CPN in female rats as a toxic endpoint.” Also, on pg 24, lines 7-9, our report states, “The SAB agrees with the EPA’s conclusions within the draft assessment report that noncancer toxicity at sites other than the kidney should not be used as the basis for deriving oral reference dose or inhalation reference concentrations.” This is difficult to reconcile with the opinion of some panel members that the kidney effects are not human relevant. Elsewhere in our report (pg. 39, lines 30-32) the possibility that kidney effects are concluded to be not relevant is acknowledged, and the EPA is encouraged to consider other endpoints.

5. As noted elsewhere, 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.

Dr. John Budroe

Cover letter page 2, 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.

3.4.4. Oral slope factor for cancer.

3.4.4.2. tBA

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 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).

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.

Dr. Marvin Meistrich

Page 22 Tier 2: The statement that "the SAB 11 recommends that the agency apply the more detailed criteria published by IARC in 1999" is not useful. That is a large, not easily accessible report. Brief examples of what criteria are being suggested should be given.

Throughout the SAB report: The statements about the uncertainties whether or not to use rat kidney effect data (particularly the male rat) leave open raised questions of EPA Draft report results. It was striking how little mention of the negative results in mice was in the EPA Draft

Report. It should be recommended (Tier 1, Line 28, Page 23) that these studies in mice, which show little or no kidney effects of these agents (e.g. chronic drinking water administration of tBA in NTP, 1995), be given more mention in the EPA report; they provide support that for the argument that the rat data may not be applicable to other species.

Dr. Jeffrey Fisher

Reading the letter to the administrator, it seems too technical and does not provide a recommendation. Can the Tier 1 recommendations be presented in the first paragraph? To me the letter says 'start over'.

Dr. Karen Chou

I have no comments at this time.

Dr. William Foster

I have no comments at this time.

Dr. Trish Berger

No comments submitted.

Dr. James V. Bruckner

No comments submitted.

Dr. Deborah Cory-Slechta

No comments submitted.

Dr. Tamarra James-Todd

No comments submitted.