

**Comments from Members of the Chartered SAB on the SAB Draft Report:
SAB Draft (12/21/2015) Review, of EPA’s Draft
Toxicological Review of Benzo[a]pyrene (September 2014)
(As of January 25, 2016)**

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Comments from. Lead Reviewers

Comments from Dr. Francine Laden

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

The SAB committee very thoroughly addressed the charge questions. They addressed each component of the questions, providing summaries of what was in the Document and providing corrections and recommendations for additional data. The committee was quite thorough and although there were many places where they praised the original document, they were at times quite critical. Furthermore, when they criticized, they provided suggestions on how to address these criticisms.

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

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

- 3) Is the draft report clear and logical?

The draft report is very clear and logical. It is well written and well presented. However, the committee is inconsistent about whether or not to pull out “recommendations” for each charge question, and when they do, these recommendations are sometimes summaries from the above text and sometimes new material. Given that the committee had a number of criticisms and suggestions, summarizing the discussed recommendations at the end of each section would be very helpful.

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

Yes – the conclusions drawn and the recommendations provided are supported by the body of the draft report.

Comments from Dr. Gina Solomon

1. Were the charge questions adequately addressed?

Yes, the charge questions were addressed very thoroughly and in great detail. It appears that the Committee did extensive work, including essentially an independent review of the literature and the underlying data. This report sets a high bar for the level of SAB scrutiny of EPA work products. Although the work of the Committee is admirable, it raises some questions about the level of detail that is necessary and appropriate for a peer review.

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

I did not identify any technical errors or omissions. The report is exceedingly thorough.

3. Is the draft report clear and logical?

Yes, the report is very clearly written. In particular, the letter to the Administrator and the Executive Summary present the issues particularly clearly and concisely.

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

Yes, the conclusions and recommendations are supported. However, the report leaves open some questions about how the Committee recommends that EPA should proceed. The B(a)P assessment has been in progress for many years, and fully addressing all the issues raised by the Committee could take several additional years. It is unclear whether the Committee views it as critical for EPA to address all the many comments in the report, and if not, which of the issues must be addressed prior to finalization of the document. Some of the issues raised seem to be ones that would improve documentation, or enhance the scientific foundation for some of the risk numbers, but they wouldn't necessarily change the risk numbers significantly; for these issues, it is unclear whether they are needed, or whether they are simply desirable. It is also unclear whether these comments are of such a magnitude that the Committee believes the report should come back for re-review by the SAB prior to finalization, or whether the report can be finalized without another SAB review. It would be helpful to have some clearer guidance for EPA on these questions.

Comments from Dr. Daniel O. Stram

1. Were the charge questions adequately addressed?

Overall the charge questions were addressed in detail throughout the document. There are many comments and recommendations for each of the charge questions. There are a number of notable disagreements between the SAB report and the EPA report. For example: The SAB report does not support EPA's conclusion that cardiovascular toxicity is not a potential human hazard. The SAB report gives additional citations of relevant scientific papers that were evidently not considered by EPA. The SAB report suggests that the keywords used by EPA in its literature search were not comprehensive enough to capture papers on this topic. The SAB report also does not support the EPA's conclusion that adult nervous system toxicity is not a potential human hazard. In both cases the SAB report is not necessarily suggesting that these outcomes (cardiovascular disease or adult neurotoxicity) are likely to be human health hazards, but is stating that the EPA review was not sufficiently rigorous in capturing all of or characterizing the quality and relevance of the scientific data. The SAB report does not support the EPA dermal slope factor (DSF) for cancer of 0.0006 per ug/day based on skin tumors in mice. The primary disagreement here is about the exclusion of studies for analysis to determine the DSF, with the primary issue seeming to be whether a study design in which application of BaP occurs less than twice per week to the animals studied should exclude a study from being considered. The SAB report makes the point that the assumption of no dose-rate effects (made by the EPA) should imply that the frequency of application should not be an

important issue, and asks for consideration of two additional studies (Nesnow et al. 1983 and Levin et al. 1977). Other points of interest are the recommendation to use an additional study in the determination of the oral slope for cancer rather than relying on a single mouse study (Beland and Culp 1998). The SAB report also indicates that developmental pulmonary toxicity also needs to be considered for a rigorous assessment not provided yet by the EPA. In these instances (points of disagreement EPA) the SAB committee seems to have done an excellent job in supporting these views and providing additional references for consideration.

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

I think there is one technical error on page 42 of the draft SAB report. This has to do with whether the Sivak data was modified by dividing by $(Le / 104)^3$. Here Le =length of exposure. My reading of the relevant part of the EPA report (page E75 and surrounding material) is that the primary data from Sivak used in the analysis of the oral slope factor was the individual animal data (time to event data for each animal) which was available from NIOSH and that no adjustment to the tumor times in this data set was made. It is only in secondary analysis of grouped data from this study that such an adjustment was made. It is also worth pointing out that the use of $(Le/104)^3$ as a divisor is based on the assumption that cancer induction is proportional to age^3 . The SAB takes issue with this divisor based on its reading of the reference to Doll 1971 given by the EPA report which indicates that multiple values of the exponent in dose have been considered. Two things seem worth pointing out. First is that in these studies, within a given treatment group, the duration (or length) of exposure is completely confounded with age. I.e. all animals are treated starting at day 0 (when they are still young) and exposure continues for the remainder of the animal's life. Thus the Le adjustment is reflecting an assumption that in these animals tumor induction follows a cubic age shape, and is not really saying that the dose response is cubic. It is only by comparing treated to untreated (or treated at various levels) that the effect of cumulative dose and the effect of age could be disentangled. The second point is that EPA has the data (from the Sivak study) to test the assumption that tumor incidence is cubic in age (or equivalently in Le), since this can be estimated for all the different treatment groups of animals and its consistency with a cubic shape judged. Therefore EPA does not need to rely upon Doll 1971 for finding an appropriate adjustment for analysis of the secondary studies. It can use data it already has.

3. Is the draft report clear and logical?

The report is highly technical, and hence very dense, but I was satisfied with its basic structure and logic

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

In general I believe that the recommendations and conclusions of the draft report are well-supported, both when the draft agrees with the EPA and also when the draft report disagrees with the EPA.

Comments from Dr. John Vena

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

I extend my compliments to the Panel for the comprehensiveness and thoroughness of their review. The review is exceptional in content and format. Explicit recommendations are made after very well written responses to the questions, thoughtful critique of the document and justification for the recommendations that follow. In my opinion all charge questions were very effectively answered, especially Charge question 3e. It is noteworthy that they developed well articulated responses and complemented them with very detailed feedback with superb comments and recommendations.

See below for specific comments and a few corrections. Clarifications are requested in the cover letter and executive summary. (see 3 below)

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

None that I can tell based on my expertise.

3. Is the Committee's report clear and logical?

The **cover letter** is concise but the text does not very effectively highlight the positive aspects of the review and the major recommendations. The letter in my view does not capture the sentiments of the full review report. There are no statements in the cover letter indicating where the SAB agrees with the assessment. The consensus advice in the letter is overall well done and specific recommendations to improve specific details of the assessment are highlighted. On page 1 line 33 it is stated "evidence presented does not support conclusion" but then the recommendation to improve the assessment is left out (also clarify related language in executive summary page 3 lines 13-16).

Page 1 line 39 What is "sufficiently strong case"? (see lines 13-16 on page 25 in body of report). The cover letter needs to be better organized as it comes across as a list of complaints. The exact recommendations should be more explicit in the cover letter and listed.

At the outset it would be good to summarize the report; the SAB was pleased with many aspects of the assessment but had concerns in the approach in the areas of hazard identification, derivation of oral reference dose(RfD) application of uncertainty factors (UF), etc. Letter should state that for the dermal slope factor recommendations were made for choice of studies, dose response analysis and dermal slope factor cross-species scaling.

The cover letter makes no mention that recommendations were made for the Literature search/study selection process and that additional literature was recommended and provided in appendix.

The cover letter does not mention that the assessment omitted adult and developmental pulmonary toxicity. Also, Appendix C is not mentioned.

The **executive summary** is well done and provides an excellent overview of answers to charge questions and recommendations. However, it suffers from the same issues as the cover letter. Page 3 lines 16-26 are awkwardly worded and need to be clarified.

The **review** is exceptional in content and format. The response to charge question 3 in particular is superb. I agree with the comments and recommendations on page 20 section 3.2.4 Cancer. The effort is impressive to list all the additional peer-reviewed studies on health effects of BaP to include in the assessment.

In addition, Appendix C with comments on the charge question format are well done and I agree and support the recommendations. (Appendix C should be noted in the cover letter and executive summary).

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes. In my opinion the report is very well written and comprehensive in responses to the charge questions.

Comments from other SAB Members

Comments from Dr. Joseph Arvai

1. Were the charge questions adequately addressed?

Yes.

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

Not to my knowledge.

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.

Comments from Dr. Kiros T. Berhane

1. Were the charge questions adequately addressed?

The charges questions were addressed adequately. The committee rightly pointed out a number of issues related to the potential over-reliance on specific studies for certain calculations, pointed out omissions in the cited literature and also suggested additional references from the peer-reviewed literature that needed to be included in the review.

In particular, I generally agree with the committee's recommendation that "the EPA review the references in the primary and secondary literature to identify potentially relevant articles not identified through the systematic searching and manual screening processes". I also agree with the comment about the restrictive nature of requiring direct measures of BaP in relation to epidemiologic studies and also the rather unsatisfactory nature of heavily relying on review (and meta-analysis) articles rather than the direct review of the primary articles. I think both need to be done (at least for key references) for a more thorough assessment.

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

No, the report has addressed all issues and/or technical errors that may not have been dealt with in the draft report.

3. Is the draft report clear and logical?

Yes, the draft report is clear, logical and has the right level of detail in pointing out issues, and has proposed reasonably detailed ways of addressing any identified issues along with potential solutions.

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

Yes, the conclusions and recommendations by the committee for the quality review are fully and logically supported by the body of the draft report.

Comments from Dr. Sylvie M. Brouder

Q1) Charge questions adequately addressed?

Yes. There were numerous and fairly detailed charge questions to the SAB CAAC & panel and, as a non-expert in this particular domain, I felt the panel did a meticulous job of sequentially addressing each charge question.

Q2) Technical errors or omissions / issues not adequately addressed?

I found the main report to be logical and did not note any major omissions. However, I wonder if the SAB should explicitly recommend that such reviews become a two-stage process with the protocol for the review including literature search strategy, selection, inclusion/exclusion criteria, etc. reviewed by "stakeholders" and the SAB prior to proceeding with actually conducting the review itself. This is a required step in the official protocols for systematic reviews with/without meta-analysis in medicine that are conducted through the Cochrane Collaborative. This would ensure that the full effort of the review itself is positioned for success from the start and could be a more efficient process in future reviews. Further, from my reading of panel responses to charge questions concerning Hazard Identification and Dose Response Analysis, it wasn't always clear to me whether the panel felt the problems with the draft toxicological review lay with the literature search-inclusion-exclusion strategy/criteria or poor interpretation of the selected papers. In the future, a two-step process for panel reviews of EPA toxicology assessments would make this sort of distinction clearer. This would also clarify use potential and/or inadequacies of

preview systematic reviews/meta-analyses. Going forward, systematic reviews should be conducted such that they can be amended and do not need to be restarted.

Q3) Draft report clear and logical?

Yes, the report is logically constructed relative to the charge questions. The narrative is fairly dense but follows each charge question closely.

Q4) Conclusions drawn / recommendations provided supported by body of draft report?

Given the great number of criticisms included in the report that are clearly substantive, it seems a summary statement in the letter to Administrator McCarthy should be included and specifically state an overall opinion by the panel on the draft toxicological review. Do the omissions and problems with the use of literature render this report inadequate or, overall, is it fairly good and a good starting place? I, myself, was unsure of the panel's general opinion on the document.

Comments from Dr. Ingrid Burke

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

Yes they seemed to be very adequately addressed. It's amazingly thorough.

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

Not that I saw.

3) Is the draft report clear and logical?

Extremely.

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

They seem to be supported at length. This is probably one of the most thorough reviews I have read of an EPA report, and it is not gratuitously complimentary, that is for sure. It is amazingly well thought through, well-referenced and critical. The summary is clear and seems very logical.

Comments from Dr. Michael Dourson

Purpose: to describe the role and involvement of chartered SAB members and Board liaisons in the quality review of draft advisory reports developed by SAB panels, subcommittees, and work groups.

1. Were the charge questions adequately addressed?

The committee was very well appointed and appears to have addressed many of the given charge questions very well.

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

Please see response to question 4.

3. Is the draft report clear and logical?

Yes, the report was very easy to read and it generally made sense.

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

Many of the conclusions seemed reasonable. Other lines of thought were not as clear. In particular,

Page 3, line 21. SAB must mean something else here, since humans do not have forestomachs.

Page 4, line 17. This occurs with many RfCs. What is SAB's recommendation?

Page 4, line 32. Very nice point!

Page 5, line 18. I would have to study this more. For example, from an exposure point of view, how can it be that the mixture exposures of Coke oven emissions are acceptable but coal tar mixture preparations are not? If the skin is not an efficient barrier in the latter case, does this not argue for comparability?

Page 5, line 26. This is based on the seminal work of Druckrey (1967), and cited in EPA (1980). See:

- Druckrey. 1967. Quantitative Aspects of Chemical Carcinogenesis. *In*: R Turhaut (ed.). Potential Carcinogenic Hazards from Drugs. Evaluation of Risks. UICC Monograph Series. Vol. 7. Springer Verlag. New York.
- U.S. EPA (U.S. Environmental Protection Agency). 1980. Guidelines and methodology used in the preparation of health effects assessment chapters of the consent decree water quality criteria. Fed Regist. 45: 79347-79357.

Page 6, line 17. But does not BAP need to be first metabolized to a genotoxic moiety? If so, what are the metabolic capabilities of this metabolism in the young. See EPA (2005), page 2-29 and the IRIS BAP text on page 1-80.

Page 13, line 15. This is a very nice discussion on gaps.

Page 13, line 32. So is this relationship causal or an association?

Page 13, line 37. Dihydrogen monoxide is also a developmental toxicant. Does SAB mean that developmental toxicity is one of the critical effects?

Page 24, line 22. Ok, so why not conduct a dual MOA dose response assessment as per EPA (2005, page 3-22)?

Page 24, line 27. This conclusion does not follow based on SAB observation of just two sentences earlier.

Page 26, line 3. And this human tissue is in an area that stores food? If not, why is the SAB concern about the forestomach in rodents?

Page 26, line 36. SAB phrases such as "sensitive health endpoint " and "human hazard" would be clearer if SAB used the parlance of critical effect, which risk assessment scientists understand.

Page 30, line 7. This RfD is close to or at the RfD for methyl mercury. Does this seem appropriate to the risk assessment folks on the SAB panel?

Page 32, line 37. This RfC is very roughly equivalent to $6 \text{ E-}7 \text{ mg/kg-day}$; the RfD is $3 \text{ E-}4$. This, 500-fold difference, if real, needs to be explained. Otherwise, it appears to be a glitch between the oral and inhalation noncancer dose response assessments.

Page 38, line 9. Unlike for noncancer dose response, the oral and inhalation cancer dose response assessments are more comparable.

Page 45, line 1. So has the SAB also concluded that BAP is a direct acting carcinogen? Or does it require metabolic activation? If the latter, then a comparison of metabolic capabilities between adult and children is needed. In fact, EPA shows evidence where children do not make as much of the metabolite, and this information argues for 1/3 the slope factor without dynamic considerations. In contrast, EPA suggests the lifetime slope factor $\times 10$ ---a 30-fold swing in the value of the cancer slope. EPA needs to address this disparity, and not using counterfactual evidence in this discussion is not helpful. See EPA BaP text, page 1-80, line 16.

Comments on EPA BaP text that might help the SAB review:

Page 1-70, figure. The MOA for tumor formation is clearly bimodal. EPA should follow its guidelines (EPA, 2005, page 3-22) and consider both MOAs in its dose response assessment. See EPA (1998) and Dourson et al. (2008) for examples.

- US EPA. 1998. Assessment of thyroid follicular cell tumors. Risk Assessment Forum. Washington, DC. U.S. Environmental Protection Agency. EPA/630/R-97/002. March.
- Dourson, M., Hertzberg, R., Allen, B., Haber, L., Parker, A., Kroner, O., Maier, A. and Kohrman, M. 2008. Evidence-Based Dose Response Assessment for Thyroid Tumorigenesis from Acrylamide. *Regulatory Toxicology and Pharmacology* 52 (2008) 264–289.

Page 1-73, line 29. From the limited information I was able to review, I see dose response concordance for adducts and tumors, but not for mutations and tumors. EPA needs to make this latter link explicit, otherwise EPA guidelines, while still dictating the use of linear dose response assessment as the default, also dictates not using the child specific adjustment factor.

Page 1-76, block “3” text about “multiple animal exposure studies.” The abstracts of these studies were not clear in describing mutation occurring before tumors. Culp et al. saw tumor incidence at the 1.0% dose; coal tar-induced cytotoxicity and cell proliferation may be critical

factors in tumor induction in this tissue. Furthermore, from the abstract this study does not appear to discuss mutations, only adducts.

Page 1-77, line 1. This write up clearly shows a dual mode of action.

Page 1-78, line 23. Note that while DNA adducts appear to be occurring before tumors in both time and dose, EPA is also suggesting that mutations are a key event; thus mutation also need to be analyzed for both time and dose concordance. Mutations clearly precede tumors in time, which is not at all unexpected. However, my brief review of the information in the SAB report and the EPA document and its supplemental information did not show that mutations precede tumors in dose. If this is indeed the case, EPA needs to clearly show this is happening. Otherwise, while a default linear MOA is still appropriately invoked, the childhood adjustment factor is not.

Page 1-80, line 16. EPA shows data that argue for 1/3 the slope factor without dynamic considerations, and yet EPA is suggesting the slope factor x 10. This difference needs to be reconciled.

Page 2-48, line 9. Perhaps these data cannot by themselves be used in a dose response assessment, but can these chemical specific data be used to replace the default values of 3 and 10 for the child-adjustment factors?

Comments from Dr. Joel J. Ducoste,

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

Yes. Document well written

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

No

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

Comments from Dr. Susan P. Felter

Overall, the Draft SAB report is well-written, follows a logical flow, and responds adequately to the charge questions posed by the EPA. I have two topics for which I have some concern, both of which are in the Dose-Response section, described in more detail below. In addition, I have a general concern that the report has many suggestions which could add significant time and cost

to the BaP assessment, and it's not clear whether these suggestions will result in meaningful improvements. I've attached a list with some page specific examples, as well as some minor editorial questions/suggestions.

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

In general, the 5 charge questions were adequately addressed. My only technical comments relate to Charge Q3 on the Dose-Response Analysis:

p. 32 ll 1-2: The SAB recommends that *“EPA consider application of a BW^{3/4} adjustment as per EPA’s 2011 allometric scaling guidance”* to support extrapolation from neonatal rodent to neonatal human. But then nothing is said about the UF for intrahuman variability. Given that the assessment is based on effects in a sensitive subgroup/lifestage, it is not clear that a default factor of 10 is appropriate. EPA’s assessment [p. 2-8, lines 17-19] states, “An intraspecies uncertainty factor, UF-H, of 10 was applied to account for variability and uncertainty in toxicokinetic and toxicodynamic susceptibility within the subgroup of the human population most sensitive to the health hazards of benzo[a]pyrene”. This is not consistent with EPA’s guidelines for risk assessment, for which a default UF-H factor of 10 is intended to cover variability across the human population. Where data are available for sensitive subgroups, this factor is reduced (e.g., see assessments for fluoride and nitrate). The SAB should comment on this.

p. 32, ll 13-14: *“The SAB also recommends that genotoxic aspects of reproductive hazard be addressed.”* Given that this is in the Dose-Response section, what does the SAB mean? Is it recommending linear extrapolation of some dataset based on the potential for a contribution from a genotoxic MOA?

p. 34, ll 1-5: *“SAB recommends that the EPA provide a brief explanation of the rationale for its selection of an allometric scaling factor for the BaP oral cancer slope factor given what is known about the BaP mode of action for carcinogenicity, reaction rates, and toxicokinetics, and specifically, how the selection of the allometric scaling factor applies when there is a portal of entry effect.”* I think this is a rather significant issue that warrants much more than a “brief explanation”.

Dermal Slope Factor (starting p. 40)

My most significant concern is that the Agency is proposing a chemical-specific DSF before the Agency has published (and had peer-reviewed) a *method* for such an assessment. Indeed, both the EPA and the SAB recognize a number of issues related to defining the most appropriate dose metric from a mouse study to apply to human exposures, and the SAB explicitly states that it does not have a specific recommendation as to dose metric, but does not feel that the EPA has provided sufficient justification for its choice of ug/day. I think it is premature to publish a DSF for any chemical before these issues are appropriately addressed and am surprised that the SAB has not made this recommendation.

p. 43 ll 9-10: *“The SAB recommends that cancer risk calculated from the derived DSF should use absorbed dose and not exposed applied dose.”* I can see a rationale for recommending this, but it is not clear in the SAB review why this is being recommended, particularly when the oral SF is based on exposure dose and not absorbed dose.

Dermal slope factor cross-species scaling (starting p. 43, line 8)

The SAB points out that, *“It is unknown if the chosen approach for scaling of skin cancer risk from BaP exposure to skin is similar to interspecies differences in whole body toxicokinetics, which is the approach (i.e., allometric scaling using $BW^{3/4}$) adopted by the EPA”* – this is another reason that a precedent should not be set for BaP before the Agency has developed a method. Since the tumors following dermal exposure are at the site of contact, the rationale for using allometric scaling ($BW^{3/4}$) is not clear.

EPA (Section 2.5.4) states that *“allometric scaling using body weight to the $3/4$ power was selected based on known species differences in dermal metabolism and penetration of benzo[a]pyrene. In vitro skin permeation was highest in the mouse, compared to rat, rabbit, and human, and was enhanced by induction of CYP enzymes (Kao et al., 1985). Using this approach, rodents and humans exposed to the same daily dose of a carcinogen, adjusted for $BW^{3/4}$, would be expected to have equal lifetime risks of cancer.”* I did not read the full EPA report, but from what I did read, I did not find the justification of $bw^{3/4}$ sufficiently substantiated. Note also that part of the rationale has to do with species’ differences in dermal penetration (mouse > human) – this would go away if EPA were to base its assessment on absorbed dose, as recommended by the SAB.

EPA goes on to say it considered several different dose metrics, which are further described in Appendix E. These result in risk estimates that vary over 3 orders of magnitude. The dose metric chosen by EPA does not include consideration of surface area of skin involved, but it is very difficult to see how this would not be an important part of how the dose should be considered given that the skin is the target organ. For example, for a total dose spread over 10 cm² of skin, the *dose to the skin* (target) spread over 50 cm² skin would be 5 times lower. I realize there are also problems with selecting this as the dose metric, which leads me again to wonder why the EPA is setting a precedent for a specific chemical risk assessment when the Agency has not previously aligned upon fundamental issues such as how to extrapolate across species.

Finally, in its response to Charge Question 5 (Public comments), the SAB states (p. 47, ll 7-9): *“With respect to the dermal cancer slope factor, the SAB supports the application of a “fidelity exercise” for proposed toxicity values to determine whether the toxicity values yield plausible upper bound risk estimates.”* It is not clear why the SAB did not raise this as a recommendation in its review of EPA’s dermal SF.

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

I do not see any technical errors. However, I see one omissions and one issue that is not adequately addressed. Both of these are also highlighted above:

1. For the RfD calculation, the SAB does not make any comment on the EPA’s use of a default UF of 10X for intrahuman variability even though the endpoint is already in a sensitive subgroup.
2. An issue that is not adequately dealt with in the draft report is that the EPA assessment on BaP is setting a precedent for calculation of a dermal slope factor before the Agency has ever

published a method for a dermal cancer risk assessment. It is reasonable to expect the Agency to establish appropriate methodology (including peer review) before finalizing a chemical-specific risk assessment. There are many complex issues that need to be addressed, especially with regard to choosing the appropriate dose metric. The SAB calls this out, but does not suggest that the EPA should not move forward with the calculation of the DSF.

3. Is the draft report clear and logical?

The draft report is logical, but it is not always clear to me what the SAB is recommending. There are many places where the SAB report says that “the Agency should consider” but sometimes it sounds like a ‘nice to have’ versus something important to the assessment.

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

Overall the conclusions drawn are supported; however, as stated above, the recommendations are not always clear.

With regard to the RfC, the SAB states: “*Regarding UFs, the EPA application of an UF of 3 to address residual uncertainty for interspecies extrapolation may be too low, since the regional deposited dose ratio (RDDR) adjustment used with the key study may not completely account for systemic toxicokinetics following an inhalation exposure.*” The basis for this statement is not clear to me. EPA has followed its guidelines, but it seems the SAB is challenging whether the guidelines are adequate. It is also not clear what the SAB means by “may be too low” (so, it may also be ok?).

With regard to the dermal slope factor (DSF), it is clear that the SAB does not feel that the EPA has adequately justified its choice of dose metric for the calculation. As the Agency shows in the supplementary materials, the choice of dose metric can result in potency estimates that are ~ 3 orders of magnitude different. This suggests to me that it is premature for the Agency to finalize a dermal SF for any specific chemical and that more work is needed first to develop methodology that should be peer reviewed. The SAB does not recommend this, but just says that EPA needs to better substantiate its choice of dose metric.

Attachment: Page-Specific Comments / Edits

I have a general concern that there are many suggestions made by the SAB that, if implemented, will add significant time and cost to this assessment and it’s not clear that they will make a meaningful difference to the assessment. Examples:

- The SAB is recommending that ~ 600 articles identified from the original search that were ultimately excluded be put into a table, grouped by the applicable exclusion criteria, and made available as supplementary information. While transparency is important, it is not clear to me that this is needed and I wonder whether it is the best use of Agency resources.
- p. 10, ll 4-6: The SAB recommends 84 addition publications “*which the agency should consider in the assessment of noncancer and cancer health effects of BaP.*” This is a long list. Has the SAB determined that these studies are impactful and is suggesting that they *should be* included, or is it suggesting that the EPA should go back and review them to determine *if* they should be included?

- p. 13, l 43-46: “*The SAB further recommends that the EPA’s literature search include consideration of the relevant windows of prenatal development...*” This is not clear. Is the SAB suggesting additional literature searching?
- p. 14, l 9-10: “... *the SAB suggests that the EPA consider including additional examples, as warranted, of mechanistic studies.*” What does “as warranted” mean?
- p. 14 ll 21-22: “*The SAB encourages the EPA to further review the literature to identify potential additional studies that may be useful in characterizing BaP-mediated developmental toxicity and dose-response relationships.*” This does not seem appropriate. A reviewer can always suggest that more literature review is needed. Is there a basis to conclude that the level of literature searching already completed is not adequate?
- p. 15 ll 6-7: “*For sub-chronic studies, it could be informative to determine if the testes had time to recover in the absence of continued exposure. ... The SAB requests that EPA consider these factors as they assess the potential for male reproductive toxicity.*” This is a broad recommendation. Are there specific studies for which the SAB is requesting additional review?

Minor Editorial Comments

p. 10, ll 24-25: “*The SAB concurs with the EPA that the available human studies support the conclusion that BaP exposure contributes to human developmental neurotoxicity.*” It is noted that the human data all involve exposures to PAH mixtures. The SAB acknowledges this later in the paragraph, but then states, “*However, the human prospective cohort studies have many strengths..*” While they do have strengths, none of them allow one to determine the contribution of BaP specifically. This statement is contrasted with text on p. 14, l 40, which is much more appropriately worded: “*exposure to PAH mixtures prevents establishing a causal link between BaP exposure and reproductive toxicity in humans, but the findings are sufficiently consistent with the effects of BaP in rodents to deduce that BaP is a reproductive toxicant in humans.*”

p. 14 l 29: “*The SAB agrees that the data support the conclusion that BaP is a male and female reproductive toxicant through oral and inhalation routes of exposure.*” The SAB is specific here about route of exposure, but not in other places. Is this intentional? Given that dermal exposure is a significant route for humans, it would be helpful to be more explicit about route-specific hazards.

p. 15 l 9: The SAB recommends here that “*EPA consider other hazard endpoints*” but the recommendation is not, in fact for other hazard endpoints; rather it is that EPA consider a possible mode of action for reproductive effects. I don’t think this belongs in the Hazard ID section.

p. 16 Recommendations (starting l 15): First bullet is MOA, not hazard ID. Second bullet has lots of “should consider” statements and it is not clear what the SAB is really asking the EPA to do. Some bullets are more relevant to Dose-Response than to Haz ID. From 4th bullet: “*The EPA may also want to consider if...*” Not clear if this a recommendation? The last 3 bullets (p. 17) refer to references that “*could be added*”. Does the SAB think they are useful additions?

p. 18 ll 9: “*Therefore the inclusion of cigarette smoking studies is not recommended for this IRIS review.*” It’s not clear if the EPA assessment included cigarette smoking studies and the SAB is

suggesting they should be removed, or if the EPA did not include them and the SAB is agreeing with this.

p. 20, ll 27-29: “*Because there is the assumption that BaP is always a component of the PAH mixtures that humans are exposed to, a logical conclusion is that BaP alone is likely to be a human carcinogen based on the epidemiologic evidence.*” I do not agree that this is not logical.

p. 24 ll 18-19: “*Lastly, 78% of the forestomach tumors induced by lifetime feeding of BaP had combined H-ras and K-ras mutations, further indicating that mutation-driven oncogene activation played a role in the etiology of these tumors.*” I don’t think this conclusion can be supported as written. What is the prevalence of these mutations in spontaneous tumors? Are there data to support that they were initiating events vs mutations that arose during progression of the tumors?.

p. 30, l 41: “*Therefore this potential relationship, albeit speculative, is potentially relevant for risk assessment.*” What should EPA do with this?

p. 32 ll 23-24: “*When possible, the EPA should identify the sensitive sex in a given study and use the sensitive sex for dose-response modeling.*” Has this not been done by EPA (in my experience, it usually is)? Is there a specific study for which this was not done?

p. 33, paragraph starting line 29: It is not clear what the SAB is suggesting here. The SAB acknowledges that EPA has followed its guidance with regard to selection of the default UF for cross-species extrapolation for noncancer inhalation effects, but then states that it is concerned about “*use of different EPA guidance documents spanning decades...*” Is there a concern that the guidance is no longer scientifically supported? Is there a specific recommendation for what EPA should do differently for the inhalation assessment of BaP?

p. 39, ll 38-39: “*The SAB recognizes that a nationwide BaP exposure assessment is far beyond the scope of the assessment, but reference to typical exposure ranges may be helpful to readers.*” I suggest that “*may be helpful*” be made into a much stronger recommendation.

p. 45, lines 25-26: “*Although the SAB has no specific advice regarding the appropriate length for the Executive Summary, the agency should strive to capture the important conclusions in a summary that is of readable length.*” It would be more helpful if the SAB could indicate whether it found this to be true of EPA’s Executive Summary (i.e., *did it capture the important conclusions in a summary that is of readable length?*)

Comments from Dr. Catherine J. Karr

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

The draft provides a highly comprehensive and complete response to the charge questions.

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

I do not identify any technical errors or omissions.

3) Is the draft report clear and logical?

The draft report is well organized and written in a clear and logical way.

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

The conclusions and recommendations are fully supported and provide clear guidance toward improving the draft Tox Review.

Comments from Dr. Sue Marty

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

- The committee adequately addressed the charge questions; in fact, the evaluation seems quite thorough. The proposed revisions by the committee would strengthen the report. More specifically, the recommendations to improve the literature search were practical. This reviewer also agrees with the committee's evaluation of the Executive Summary (i.e., the summary gives an appropriate presentation of key points from the assessment). The committee adequately justified their endorsement or disapproval (i.e., inadequate support) of selected endpoints as the basis for deriving RfD/RfC values for BaP and in some cases, gave quite detailed information when the committee had an alternative viewpoint. The request to better leverage toxicokinetic and mechanistic data in interpreting toxicity studies is sound advice. The suggestions to better describe key assumptions and uncertainty are well supported too. The conclusions of the review committee are clearly and consistently expressed in the Letter to the Administrator.

- It is reassuring that many of the conclusions in the EPA BaP document were supported by the review committee, particularly given that the human evidence is largely rational rather than empirical (e.g., p. 20, l. 26-27; "from the epidemiologic studies, there is no direct evidence that BaP alone is carcinogenic"). The applicability of EPA Criterion 2 on p. 21-23 was useful to support the "human carcinogen" designation. However, given that much of the core health effects are derived from a rational alignment of available data, it may be useful not to speculate more than necessary on other effects, which may be even further removed from empirical data (e.g., link between BaP exposure and preterm labor on p. 30, l. 39-41).

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

- On p. 24, l. 40-41, the reviewers suggest the addition of a table describing the characteristics and nomenclature of the various methodologies used for BPdG and PAH-DNA adduct formation. This is a good suggestion. The table should include information on the specificity of adducts as an indicator of BaP exposure.

- The application of epidemiology data to the BaP review requires the use of data from PAH mixture studies to assess BaP health impacts. If possible, it would be useful if the authors developed a summary table to describe the different industries referenced (coke oven workers, aluminum smelter workers, iron/steel founding, etc.), what is known about

PAH exposures (e.g., estimated ranges, means/medians) and what, if anything, is known about BaP exposures in these groups (estimated proportion BaP). It is not clear in the report that increased cancer incidence (and other adverse health effects) are related to greater rates of PAH/BaP exposure in the industries cited (i.e., are coke oven workers more exposed than asphalt workers or foundry workers?). Cigarette smoking could be added to the table too as the report authors have a mixed approach to using these data [i.e., there are multiple other constituents in cigarette smoke that contribute to health effects, yet in some cases, this appears to be the example cited to indicate that BaP may be having an adverse health effect (e.g., female reproductive effects – ovulation disorders, ovarian senescence, etc.)]. Perhaps even food exposure levels could be estimated. A table such as this, placed early in the document, could help the reader appreciate the relationship between BaP and PAH mixtures in epidemiology studies and provide a better understanding on the assumptions made by the reviewers (i.e., that BaP is a substantive contributor to adverse effects).

(p. 18, l. 28-31) Check sentence structure.

(p. 24, l. 44-47; p. 25, l. 1-5) This passage identifies some sections of the report where the committee has requested clarification to address vague/inaccurate text. There are other sections in the BaP report where minor additions would greatly clarify the value of the experimental data referred to in the text. For example, in neurobehavioral studies, it would be helpful to add a phrase as to whether data from various studies were collected ‘blind to treatment group’ to help the reader appreciate the robustness of these data. Consider requesting the phrase ‘controlled for stage of estrous’ when describing animal studies that examined hormone levels, reproductive organ weights, and histopathology in females (unless after reproductive senescence). Some of the data sets (e.g., Chung et al., 2011) saw effects at very low dose levels relative to other studies. Consider requesting a statement on whether analytical verification of dose levels was conducted.

3) Is the draft report clear and logical?

- (p. 1, l. 36-38; p. 9, l. 1-3) Consider modifying the statement, “The SAB finds requiring a direct measurement of BaP exposures unnecessarily restrictive, especially in regards to epidemiology studies as these studies could be relevant as supplemental information for hazard identification”. It is important to be clear that epidemiology studies that measured BaP/PAH exposure or DNA adducts are of greater value (Tier 1) when examining hazard/risk than studies that did not evaluate exposure (Tier 2). On p. 9, l. 1-15, there is a comment that these Tier 2 studies versus Tier 1 studies, so presumably, this is the intent of the original comment. This may also require an edit on p. 20, l. 37-45 to differentiate the value of these studies.

- (p. 11, l. 8) The discussion of the developmental neurotoxicity studies on page 11 is very well done. A minor comment...could the authors add a phrase to explain the advantage of “1) using in-house breeding”? In some cases, in-house breeding programs result in differences in strains that can contribute to difficulties with data reproducibility. Perhaps in-house breeding was recognized as an advantage because it allowed exposure to begin at an earlier stage or possibly because it alleviated shipping stress. Could the reviewers please add this detail?

- (p. 13, l. 15-29) There is a good discussion on gaps in exposure periods relative to brain development when evaluating developmental neurotoxicity. The reviewers acknowledge a gap from PND 14-21, which is consistent with exposure requirements for DNT studies. Is it worth incorporating a statement that brain development actually extends beyond this period, which also could be meaningful when assessing the gaps in developmental neurotoxicity data?

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

- Without re-examining the individual studies in detail, the conclusions drawn by the reviewers seem reasonable and well supported. Furthermore, the authors have provided good justification for their recommendations, including explanatory text and additional references. These recommendations merit consideration by the EPA during its revision of the *Toxicological Review of Benzo[a]pyrene* document

Comments from Dr. Kristina D. Mena

1. Were the charge questions adequately addressed?

Yes

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

No

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, the Committee identified and discussed some very important concerns related to the literature search strategy; I recommend these concerns be included (or at least summarized) in the letter to the Administrator.

Comments from Dr. Surabi Menon

Q1: Were the charge questions to the committee adequately addressed?

The charge questions appear to have been addressed thoroughly. It includes suggestions to additional reference and sampling as well that when included could make the study more robust.

Q2: Are there technical errors or omissions or issues that are not adequately dealt with in the draft report?

This is not a technical area I am familiar with. That being said, there has been a level of thoroughness applied that suggests there may be no big omissions or issues with the assessment.

Q3: Is the draft report clear and logical?

It appears clear and logical, but would be useful to categorise the recommendations in a more defined manner and in brief, as for example the recommendations outlined for Charge Question 2c or as reported on page 43.

Q4: Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Almost all of the conclusions or recommendations suggested appear to be well supported by evidence either in the form of other studies or references or additional approaches or guidance that could make the conclusions more grounded.

Comments from Dr. James R. Mihelcic

Quality Review of Draft SAB Report on the IRIS Toxicological Assessment of Benzo[a]pyrene

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

Yes, the charge questions were adequately addressed.

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

I did not identify any technical errors or omission or issues in the draft report.

3) Is the draft report clear and logical?

The report is clear and logical. There is a lot of detail and recommendations in the draft report that are organized, referenced to peer literature, explained in easy to understand language.

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

Yes

Comments from Dr. H. Keith Moo-Young

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

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

No.

3) Is the draft report clear and logical?

Yes. The report is well written.

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

Yes.

Comments from Dr. Kari Nadeau

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

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?— it was very thorough and additional references as well. If possible, it would be helpful to have read Appendices D-G.

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

Comments from Dr. Tara L. Sabo-Attwood

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

There were 4 Charge Questions presented to the committee, some with several sub-parts. Overall, the committee provided a comprehensive and thorough report and answered the charge questions effectively, providing several recommendations as appropriate.

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

No, I did not identify any technical errors or omissions/issues in the report based on my area of expertise.

3. Is the draft report clear and logical?

Yes, overall the report is well written and organized. Some sections have a subheading 'recommendations' (e.g. 3.2.3. Immunotoxicity) whereas other sections provide recommendations within the body of the report without this subheading (e.g. Other Toxicity). A titled 'recommendation' subheading would help to streamline dense areas of text and provide clarity where appropriate.

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

Yes, in general the conclusions and recommendations are supported by the report. A few lines of text were vague or required minor edits;

Page 3 Line 2 “It is likely that the developing immune system is more sensitive to BaP exposures than adult exposures”. It is not clear if this is a general statement that applies to all aspects of development or that it is based on evidence from the literature that provides specific immune-based evidence. The same text is also used on Page 19 Line 19.

Page 17 Lines 23-25 “Some of these mechanisms are similar to cancer initiation and promotion, and there may, in fact, be a relationship between the carcinogenicity of certain PAHs, such as BaP, and their immunotoxicity”. This statement may also be relevant to the relationship between immunotoxicity and other effects discussed, such as reproductive effects, that are non-carcinogenic in nature.

Page 6 - Space needed between lines 14 and 15

Comments from Dr. Jay Turner

1. Were the charge questions to the committee adequately addressed?
The charge questions are thoroughly and adequately addressed. Suggestions on the format of charge questions (Appendix C) are appropriate and constructive.
2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
*Not to my knowledge but I did not thoroughly review the draft toxicological assessment which is the focus of this draft SAB report. *
3. Is the draft report clear and logical?
The draft report is clear and logical with adequate details for each recommendation.
4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Yes, conclusions and recommendations are detailed in the body of the draft report with counterbalancing discussions and references as appropriate.

Comments from Dr. Charles Werth

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

Yes, the charge questions were adequately addressed. Responses to the charge questions are generally very clear and informative, and provide excellent guidance in terms of how to address deficiencies in the Draft Toxicological Review of Benzo[a]pyrene.

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

In general, I did not identify any technical errors or omissions.

One issue on my mind while reading the report was whether the toxicological effects of BaP in a mixture are worse than BaP alone (synergistic effect). I did not see any text on this issue, and am bringing it up to confirm that no studies support such an effect.

3) Is the draft report clear and logical?

Generally the report is clear and logical. Below are instances where clarification or rewording may be needed to improve understanding.

Letter to the Administrator, First Page, Lines 33-35: The text reads “the evidence presented in the assessment does not support EPA’s conclusion that forestomach toxicity in rodents, cardiovascular toxicity, and adult nervous system toxicity are not potential human hazards.” I don’t think the authors are saying that forestomach toxicity in rodents is a potential human health hazard. Instead, I think they are saying that it could indicate a potential human health hazard through a similar mode of action (i.e., humans don’t have a forestomach).

Executive Summary, Page 1, lines 20-26: The text reads “The SAB recommends that the EPA review the references in the primary and secondary literature to identify potentially relevant articles not identified through the systematic searching and manual screening processes. In addition, secondary literature searches should be conducted whenever evidence for additional effects (e.g., cardio) and specific data gaps emerge.” Is primary literature what is identified through initially selected key words, and secondary literature what is identified through key words identified in the primary search? Also, the phrase “potentially relevant articles” seems too open ended. Could more direction be given?

Main Report, Page 30, Lines 43-44: The text states “The SAB further recommends that (2) the EPA conduct the appropriate literature reviews (as necessary) to support either inclusion or exclusion of endpoints for RfD determination.” This statement is a bit vague, and perhaps condescending (when written so broadly). Could it be reworded to more accurately describe what the SAB is recommending.

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

Generally, the conclusions and recommendations are very well supported by the body of the draft report. Below is one instance where a recommendation might be expanded.

Executive Summary, Page 1, Lines 36-39: The text reads “The SAB found that requiring a direct measure of BaP exposure is unnecessarily restrictive, especially when evaluating epidemiology studies, as these studies would be relevant for hazard identification. Epidemiological studies of

coke oven workers and other occupational groups with known exposures to BaP should at least be reviewed in the tables if not the text.” Details provided in the body of the report provide strong justification for this text. I’m not a toxicologist, and I don’t know if it’s reasonable, but I wonder if it’s possible to go a step further and protect human health by defining exposure limits for products containing BaP. For example, coal tar is used to sealcoat roofs and pavements, and contains BaP. Industry workers are continually exposed through inhalation of vapors, and also dermal contact. Is it possible to define health-based exposure limits for this product?

Comments from Dr. Robyn S. Wilson

1. Were the charge questions adequately addressed?

Yes, the report was well-written and provided a thorough response to each of the charge questions.

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 did not see any errors or omissions, or issues that were not adequately dealt with in the draft report.

3. Is the draft report clear and logical?

Yes, I found the report quite readable and clear.

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

Yes, as mentioned above, the report was quite logical and the conclusions drawn were clearly supported by the body of the report, more specifically by the primary literature cited as the basis of the recommendations.

Alignment and consistency of the message: I found that the messages in the report were well-aligned throughout the document. Specifically, that the conclusions supported by the SAB, and those that the SAB felt needed to be revisited were clearly highlighted throughout the cover letter, the executive summary, and the body of the report. Although clearly all of the recommendations and conclusions cannot be highlighted in the abbreviated summaries, there was no inconsistency across the various piece of the report.

Comments from Board Liaisons

Comments from Dr. Stephen J. Klaine

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

Yes. Document well written

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

No

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