

**Preliminary Comments from Members of the Chartered SAB on the report,  
*SAB Review of EPA’s “Development of a Relative Potency Factor (RPF)  
 Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February  
 2010 Draft)”***

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## Comments from lead reviewers

### Comments from Dr. Jana Milford

1. Were the original charge questions adequately addressed?

Yes. The panel did a very good job of addressing each of the charge questions, and/or explaining why some of the charge questions were not well posed.

However, one suggestion by the panel seems to go beyond the scope of the review – the recommendation that EPA “support research to develop a suite of short-term assays and biomarkers” (p. 8, lines 38-40). Perhaps the panel could explain better what research they are seeking and how it would aid in assessing cancer risk for PAH mixtures.

2. Are there any technical errors or omissions?

I did not identify any.

3. Is the committee’s report clear and logical?

I generally found the main body of the report to be clear and logical. I especially liked the illustrations provided in the response to charge question 5. However, as detailed below, some of the panel’s comments warrant further explanation, and some items are treated somewhat inconsistently under different charge questions. Some statements in the executive summary are too abbreviated to be clear.

p. i, line 43. The statement that the scientific basis for the RPF approach was not found well justified warrants clarification. It is not clear in the letter whether the panel thinks EPA’s justification was poorly explained, or whether the panel doesn’t think the RPF approach *can* be justified from a scientific perspective. Later in the report, the panel explains that there is evidence for interactions in PAH mixtures, which EPA’s additive model neglects. Nevertheless, the panel believes this simplification is appropriate as a practical matter. This is an important point that should be explained better in the letter to the Administrator.

p. ii, lines 7-8. It would be helpful if the panel would briefly explain the current status of the B[a]P assessment.

p. 1, lines 40 – 43. This mention of the panel’s view of the two assumptions that EPA says underlie the RPF approach is incomplete. The organization of the executive summary would be improved by incorporating the second and third bullets on p. 2 into this paragraph, as they provide the needed explanation.

p. 3, lines 18-23. The panel should clarify whether it is looking for more justification of the linear model or recommending use of a nonlinear model instead.

p. 3, lines 34-35. The panel’s “concern” about use of high BMR values begs the question of what they recommend in case those are the only data available for a particular compound.

p. 3, lines 36-37. This bullet needs to be expanded to better explain what the panel is seeking.

p. 4, lines 21-22. This bullet needs further explanation.

p. 4, lines 34-35. Please consider the underlined addition to this sentence: “The agency is encouraged to continue evaluating other methods to combine RPF values across studies ...”

p. 8, lines 10-11. This statement warrants further explanation.

p. 9, lines 4-7. The comment that adequate context is not provided conflicts with the panel’s response to charge question 7 (pp. 28-29) which says the context is adequately described, but the description should be moved up to earlier in the document.

p. 10, lines 5-12. I think it would be helpful if the panel could identify the “results” or at least some example studies that suggest that interactions occur with PAH mixtures.

p.12, lines 19-30. I’m wondering if the panel could more clearly explain its argument that “the RPF method is completely independent of, and does not require any mechanistic understanding so long as there are good animal bioassay data that can generate a slope for an RPF comparison to BaP.” It may be that deriving RPF values doesn’t require any mechanistic understanding, but doesn’t the accuracy of the approach depend on other PAH having dose-response relationships that can be represented as a constant multiplier of the relationship for BaP?

p. 13, lines 26-28. I think it would be helpful if the panel would identify what additional “quantitative information” it is seeking.

p. 25, lines 32-43. The discussion in this paragraph raised the question of what EPA does when it can’t develop an RPF value for a particular compound. Is the default in that case an assumption of zero risk, or is some typical value assumed? In other words, what are the implications of recommending that no RPF be calculated if only single dose studies are available?

p. 26, lines 5 – 12. It isn’t clear whether the panel is recommending consistent use of geometric means in lieu of arithmetic ones, or case-by-case consideration of which is most appropriate. If arithmetic means are used, does the panel also recommend that they be calculated using inverse square weighting?

p. 29, lines 27-33. If I understand correctly, this paragraph addresses the same issue as that addressed on p. 26, lines 5-12. If that’s the case, the two paragraphs could be better reconciled for clarity.

4. Are the conclusions and recommendations supported by the body of the Committee’s report?

Generally, yes. However, please see the response to question 1 – the recommendation on p. 8, lines 38-40 is not supported.

## Comments from Dr. Eileen Murphy

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

Charge Question 2: The Panel gave much thought to the charge question here and I agree with their assessment that 2.a is actually two questions, an important distinction. By separating the issue of the scientific basis of the RPF approach from the practical issue of using the RPF approach, the Panel is providing EPA with significant information about the RPF methodology while advising the agency about other potential preferable methodologies (that may not be ready for practical reasons at this time). Overall, the Panel provided thoughtful and insightful recommendations to these charges.

On page 12, lines 19-30, under charge question 2.c., this paragraph seems to address charge question 2.a rather than 2.c. (adequate justification for using RPF as scientifically defensible rather than 2.c., which is whether the weight of evidence that PAHs have a similar mode of action).

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

No.

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

Yes, their recommendations are presented very clearly and logically for the most part. Somewhere, it would be good to state that the original charge questions are in italics. I was confused and had to go to the main webpage because it was not clear to me whether these were the charge questions or summaries from the Panel. Very well written and easy to follow.

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

Yes, conclusions are supported and fully explained and supported with literature.

Editorial:

The Executive Summary is somewhat long. I suggest removing the minor recommendations (i.e., sections that begin with "Additionally, the Panel has the following...." The report is not overly long, and the executive summary should reflect the length of the report. So, for a 24 page or so report, the executive summary should be 2-3 pages. It is currently over 5 pages.

## **Comments from Dr. Stephen Roberts**

The Panel reviewed a very large and complex report, and was tasked with responding to an extensive list of questions. They conducted a very careful, thorough review, and have provided guidance that should be quite valuable to the Agency.

### **Quality Review Questions**

#### **Were the original charge questions adequately addressed?**

For the most part, the answer is “yes,” with the principal findings and recommendations clearly indicated. However, among the several, multi-part charge questions, a few of the questions don’t seem to be answered clearly.

#### **Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee’s report?**

Two aspects of the report that require some additional explanation, in my opinion, are criticism of the assumption of a common mode of action and the recommendation that the Agency pursue a whole mixtures approach.

#### **Is the Committee’s report clear and logical?**

Yes. Some rearranging and tightening of material would improve presentation, however.

#### **Are the conclusions drawn or recommendations provided supported by the body of the Committee’s report?**

Yes. The recommendations are logical extensions of discussion provided by the Panel.

### **Detailed Comments**

#### **Cover Letter to the Administrator**

My philosophy is that the cover letter should be short and highlight key aspects of the review that merit the Administrator’s attention. This letter accomplishes that, focusing on the high points of the review and the “big picture.”

#### **Executive Summary**

Charge questions are omitted from the Executive Summary, and the reader is referred to an appendix where they appear. Not listing the charge questions in the body of the Executive Summary makes it easier to create a set of comments and recommendations that flows well, but makes it difficult for the reader to assess [based solely upon reading the Executive Summary]

whether the questions were actually answered. There are some casualties in this regard; for example, the answer to question 1b is missing from the narrative in the Executive Summary. When discussing how chemicals produce effects, the US EPA has some rather clearly defined terms, such as “mode of action” and “mechanism of action.” As a general comment, these terms are not always used correctly in the review document, I think. The Executive Summary seems to try to avoid this by talking about chemicals that “act in a similar toxicological manner” (see page 1, lines 41-42; page 2, lines 14-15; and elsewhere). The meaning of this phrase isn’t clear (at least to me), and I recommend either defining it or substituting mode of action or mechanism of action as appropriate.

## **Body of the Review Report**

### **Charge Question 1**

Although the title of the first charge question includes the phrase “Overall Scientific Soundness,” the questions posed actually ask about clarity of presentation. The first paragraph of the response addresses these questions, but the rest of the rather extensive discussion in the response provides information that is more appropriate to other charge questions (and is in fact redundant with responses to those questions). I recommend working this text into later responses or eliminating it.

If this text is left in, please remove reference to “real world” samples and mixtures. Also, the paragraph on lines 38-40 is cryptic and seems unrelated to both the charge question and the point about evaluating mixtures directly.

### **Charge Question 2**

I think that the discussion of modes and mechanisms of action needs to be tightened a little bit. For example, on page 9, lines 35-36, it states that chemicals are assumed to act by the same mechanism of action when a relative potency factor (RPF) approach is applied. I think that the assumption is actually that they have the same mode of action. This is carried over on to the next page (line 3). The response to 2c suggests that if chemicals are found to have different precise mechanisms of action, this weakens support for an assumption that they have the same mode of action. Chemicals do not have to have the same mechanism of action to have the same mode of action.

As I read the report, the Panel strongly contends that the RPF method can be used for any set of chemicals regardless of mechanism/mode of action as long as the endpoint is the same (e.g., cancer). It is, of course, more complicated than that. Inclusion of chemicals in an RPF framework does not have to be biologically-based (i.e., mode of action) and could be empirical based upon fit to the same dose-response model. There are some drawbacks to both approaches, which aren’t well developed in the discussion. I think this aspect of the report needs some work. The possibility of movement to a whole mixtures approach is recommended in response to Question 2 and elsewhere. The paragraph that starts on page 13, line 4, covers nicely the complexity inherent in PAH mixtures, not only with regard to PAH composition, but also a myriad of other chemicals that can potentially affect PAH toxicity. It is, as the response points out, impossible for an RPF approach to capture this complexity. On the other hand, this complexity makes the number of mixtures to be studied almost infinite, which is also

impractical. To help explain why moving to a whole mixture approach might be a reasonable proposition, it would help to explain how testing some reasonable number of mixtures might work. Otherwise, this recommendation runs the risk of being labeled as naïve.

### **Charge Question 3**

It would be helpful to provide an example of the additional quantitative information being requested.

### **Charge Question 4**

No suggestions

### **Charge Question 5**

The response should probably start with a sentence clearly responding to the first question.

### **Charge Question 6**

No suggestions

### **Charge Question 7**

It is not clear that the first question in 7c is answered. For 7d, I could not find a response to the request for comment on whether alternative methods exist. For 7e, the first question does not appear to have been clearly answered.

### **Charge Question 8**

The third paragraph is redundant with information presented elsewhere. Also, the paragraph that begins on line 20 on page 31 appears elsewhere as well. Perhaps a cross reference would be better.

### **Charge Question 9**

No suggestions.

### **Editorial Suggestions:**

Pg 1, lines 25-28, “The Panel agrees ...”: This is a run-on sentence. I suggest breaking it up for clarity.

Pg 2, lines 16-17, “... a stronger argument should be made ...”: The meaning of the last half of this sentence isn’t clear.

Pg 2, line 42: substitute “a target PAH” for “the target PAH”?? Presumably the statement can apply to more than one PAH.

Pg 3, line 12 and line 18: comma after “i.e.”

Pg 3, line 34: "BMR" should be defined here

Pg 4, line 4: replace "between" with "among"

Pg 4, line 26: comma after "e.g."

Pg 5, line 10: shouldn't this be "e.g." instead of "i.e."?

Pg 8, lines 13-16: run-on sentence.

Pg 10, line 29: replace "pursue" with "continue"?

Pg 12, line 40, "... based upon BaP as a single agent.": Does this mean based upon BaP content alone or based upon BaP as the index chemical?

Pg 12, line 42, "both scientific ...": This is a little vague, as only one assumption is being discussed.

**Comments from Dr. Paige Tolbert**

The following comments are provided in my role as discussant/quality reviewer of the report by the SAB Polycyclic Aromatic Hydrocarbon (PAH) Mixtures Review Panel reviewing EPA's "Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February 2010 Draft)."

**Quality Review Question #1: whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed.****Response:**

The SAB Panel has adequately addressed the original charge questions posed to them by EPA.

The panel was asked a series of questions regarding the rationale for recommending an RPF approach, the previously published RPF approaches, evaluation of the carcinogenicity of individual PAHs, methods for dose-response assessment and RPF calculation, selection of PAHs for inclusion in the RPF approach, derivation of RPFs for selected PAHs and uncertainties and limitations associated with the RPF approach.

The Panel has provided a thoughtful and thorough response to each charge question. Key responses include the following:

- The panel does not find the scientific basis for the RPF approach to be well justified, in particular the assumption that there are no interactions among the PAHs at the low environmental exposure levels. The panel recognizes, however, the pragmatic need for the approach given the data currently available and therefore generally agrees with EPA's decision to use of the RPF approach. This reviewer agrees with this assessment.
- The panel agreed with the choice of benzo[a]pyrene as index compound, but suggests that the cancer slope factor for this compound be updated. This reviewer agrees with this recommendation.
- The panel felt that the EPA decision to include only studies in which the index compound (benzo[a]pyrene) was simultaneously studied with the compound of interest was unnecessarily restrictive and that EPA could also make use of studies that simultaneously tested another compound for which there was existing information on the potency relative to benzo[a]pyrene. To this reviewer, this suggestion seems to be a logical way to extract more information from the existing data, as long as the compounding of uncertainties can be accounted for.
- The panel proposes that EPA seeks support from NTP and/or others to undertake animal bioassays of 12-15 selected mixtures as part of a strategic initiative to move toward a whole mixture approach. In proposing this, this reviewer feels it would be helpful to clarify whether the panel considers that these results would be applicable only to those mixtures selected or would be useful for generalizing risk assessment to other mixtures beyond those selected, with additional PAHs or with differing proportions of the same PAHs.

**Quality Review Question #2: whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report**

**Response:**

This reviewer did not find technical errors, omissions or issues that are inadequately dealt with in the report.

**Quality Review Question #3: whether the Committee's report is clear and logical**

**Response:**

This reviewer finds that the Panel's report is clear and logical. The report effectively communicates the Panel's assessment of the draft report with respect to EPA's charge questions.

Some very minor comments:

The following text in the Executive Summary is unclear: "Despite these concerns, in recognizing the pragmatic need for the RPF approach and completion of the document, the Panel recommends including a discussion on EPA's previous considerations about implementing a whole mixtures approach and the rationale behind the decision to pursue the RPF approach." The statement is difficult to follow (and completing the document is not a goal in itself.)

In several instances, the Panel report refers to "quality studies" (e.g., p 14) – this ambiguous terminology should be avoided to prevent confusion regarding whether the authors are referring to studies addressing quality or studies of high quality.

Suggest editing the following sentence on p. 13 to specify the type of quantitative information that should be added: "This chapter adequately summarizes the previous RPF approaches but could be improved by providing more quantitative information, and editing Table 3-1 to..."

p. 28 "Also, the Panel makes several recommendations for calculating RPFs;" – it would help to state where these recommendations are (cross-reference text).

**Quality Review Question #4: whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report**

**Response:**

The conclusions drawn and recommendations provided are supported by the body of the Panel's report. Overall, the Panel's conclusions and recommendations are scientifically sound and well-justified.

## Comments from other SAB Members

### Comments from Dr. Timothy Buckley

1. Some suggested edits to provide clarity re letter and ES are provided below. The comments below are also captured in the suggested edits.
2. The suggestion “that EPA pursue developing a whole mixtures approach for PAHs” seems to be outside of the scope of the charge questions and confuses the panels position on whether EPA should use the RPF approach.
3. Similarly, the Panels position on the “Rationale for Recommending an RPF Approach” is confused by its mention of the “whole mixtures approach” within its recommendation “. . . including a discussion on EPA’s previous considerations about implementing a whole mixtures approach and the rationale behind the decision to pursue the RPF approach.”
4. It is stated that the Panel “does not find the scientific basis for the proposed RPF approach to be well justified in the document” and then goes on to support this position based on uncertainty with respect to two underlying assumptions, but it isn’t clear if the Panel is suggesting an alternative better approach. As currently written, it sounds like the Panel is identifying a point of uncertainty rather than addressing the charge question as to the rationale for the RPF.
5. In response to charge question relating to the Rationale for Recommending an RPF Approach, the Panel recommends "including a discussion on EPA’s previous considerations about implementing a whole mixtures approach and the rationale behind the decision to pursue the RPF approach." Do we infer from this that EPA has not provided an adequate rationale for the RPF approach? If so, better to say directly rather than to confuse the issue with a discussion of the whole mixtures approach.
6. In suggesting “emphasizing comparisons of actual cancer bioassay data” it would be useful to provide an example of what this would look like, i.e. exactly what might be compared.
7. Does it make sense to recommend “editing Table 3-1 to use a standard approach for reporting values (same significant figures, scale, etc.)” when Table 3-1 is simply a compilation of reported RPF values. Is the Panel suggesting that EPA edit what has been reported in the literature?
8. For the recommendation “The Panel recommends that once a study is considered to have sufficient quality, the variability of study design characteristics between studies be carefully considered prior to inclusion in the RPF calculation” it would be good to provide EPA with guidance as to how this could be practically achieved.

#### Edits to Administrators Letter

However, ~~there is a need to strengthen Panel does not find~~ the scientific justification basis for the RPF approach. ~~to be well justified in the document. Nevertheless, T~~ the Panel recognizes the practical pragmatic need for the RPF approach, and based upon the currently available data,

generally agrees with ~~its EPA's use of the RPF approach~~ for assessing PAH mixtures. The Panel agrees with EPA's decision to update the 1993 approach by increasing the number of compounds ~~in the approach~~, and including the most recent data in calculating and expanding the RPF values. ~~for PAHs.~~ The Panel encourages the Agency ~~to complete this document and has recommendations~~ to strengthen the document with respect to with regards to the 1) selection of studies, 2) methods for dose-response modeling, and 3) calculations of final RPFs.

The Panel agrees with EPA's selection of benzo[a]pyrene (BaP) as the index compound for the RPF approach. However, the current cancer slope factor for BaP is outdated and in order to estimate the risk of PAH mixtures, an up-to-date cancer slope factor for BaP is essential. The Panel urges the Agency to quickly finalize the BaP assessment.

The Panel recommends that EPA pursue developing a whole mixtures approach for PAHs. The Agency should set this as a strategic initiative, with a specific timeline and benchmarks, that lays the foundation for an underlying concerted research program. The Panel recommends that the Agency seek support from the National Toxicology Program (NTP) and/or other entities to test a portfolio of 12-15 different complex PAH mixtures, using animal bioassay studies. These complex PAH mixtures should represent a diverse array of mixtures, but also represent the most important PAH mixture classes of concern to EPA. The Panel believes that, with these data in hand, EPA could then potentially validate the RPF approach and could also potentially replace the RPF approach for assessing cancer risk of PAH mixtures. [this sounds good but seems outside the scope of the charge questions.]

#### Executive Summary

“The Panel recommends that EPA pursue developing a whole mixtures approach for PAHs to potentially validate the RPF approach and to serve as a possible replacement for the RPF approach in the near future. The Panel recommends that the Agency seek support from the National Toxicology Program (NTP) and/or other entities to test a portfolio of 12-15 different complex PAH mixtures of concern to EPA, using animal bioassay studies.” [this is outside of the scope of the charge questions and can be interpreted as a condemnation of the current RPF approach. This specifies a research agenda which is not what EPA was asking for.]

#### *Rationale for Recommending an RPF Approach*

~~EPA's document presents the scientific rationale for recommending an RPF approach for PAH mixtures.~~ The Panel does not find the scientific basis for the proposed RPF approach to be well justified in the document. There are two basic assumptions that are proposed for applying the dose-additivity model used in the RPF approach: that the PAHs in the mixture act by a similar toxicological manner and that no significant interactions occur at low, environmentally relevant doses. The document itself cites data that call into question both of these underlying assumptions. The document discusses a number of other uncertainties that further undermine the logical and scientific basis for the assumptions on which the RPF method is based. [This is unclear. Is the panel suggesting that there is an alternative more scientifically justifiable approach? It is one thing to identify uncertainty and quite another to suggest that there is sufficient evidence to support an alternative approach.]

Despite these concerns, in recognizing the ~~pragmatic-practical~~ need for evaluating toxicity of PAH mixtures ~~the RPF approach~~ and completion of the document, the Panel recommends including a discussion on EPA's previous considerations about implementing a whole mixtures approach and the rationale behind the decision to pursue the RPF approach. [this is at the heart of the charge question so do we infer from this that EPA has not provided an adequate rationale? If so, better to say directly.]

Additionally, the Panel has the following comments and/or recommendations:

- The Panel finds that the choice of BaP as the index chemical is well justified and is appropriately described for this RPF approach. The Panel urges the Agency to quickly finalize the BaP assessment.
- The Panel recommends that the assumption that PAHs, as a class, act in a similar toxicological manner should be de-emphasized as a rationale for using the RPF approach and that a stronger argument should be made for emphasizing comparisons of actual cancer bioassay data. [it would be helpful to specify what it is that you are suggesting comparing. CSF? What else?]
- The Panel finds that EPA's assumption that interactions among PAH mixture components do not occur at low levels of environmental exposure is not scientifically well justified. However, in the absence of data that support a specific interaction (additive, sub- or super-additive, etc.), a default assumption of additivity is a reasonable assumption for the purposes of the RPF analysis. [This seems inconsistent with the paragraph above.]

#### *Discussion of Previously Published RPF Values*

EPA presents a background on how RPFs have been derived in the past. The Panel believes that the document adequately summarizes the previous RPF approaches, but could be improved by providing more quantitative information [would be helpful to provide an example], and editing Table 3-1 to use a standard approach for reporting values (same significant figures, scale, etc.). [Does this make sense if summarizing what has been reported in the literature?]

#### *Evaluation of the Carcinogenicity of Individual PAHs*

EPA discusses the development of a database of primary literature and the criteria used to include or exclude studies. Based upon the initial literature search, a list of 74 PAHs was evaluated. The Panel finds that the list of 74 PAHs is reasonable and that the database of primary literature appears adequate, but recommends that a recently published IARC Monograph on PAHs, Volume 92, be added ~~to the database as an additional resource~~ (IARC, 2010).

One of EPA's study selection criteria is the stipulation that BaP must be tested concurrently with the target PAH being considered. This restriction raises the concern that quality animal bioassay studies may be dismissed. The Panel recommends that EPA consider exploring an approach where the target PAH that was tested with BaP could serve as a surrogate for BaP in studies where BaP was not tested concurrently. This may allow for additional quality

studies to be included. However, in considering this alternative approach, EPA should also take into account factors that could potentially outweigh the benefits in the establishment of a RPF for a specific PAH, such as cross-study and cross-laboratory comparability issues.

The Panel believes that a quality assessment should be done for each individual study. The Panel recommends including information such as sample size, dosing, mortality (prior to tumor development), test compound purity, and whether or not the data utilized are derived from tumor incidence or multiplicity.

#### *Methods for Dose-Response Assessment and RPF Calculation*

EPA presents the selection of dose-response data and methods for dose-response assessment and RPF calculation. For quantal data (i.e. tumor incidence), EPA used the multistage cancer model. The Panel agrees with EPA's use of the multi-stage cancer model for quantal data, but has specific recommendations on the parameterization of the model. [\[what are the recommendations?\]](#) The Panel also recommends that EPA provide further detail on the assumptions regarding the distribution of data and further detail on the parameterization of the model.

For continuous data (i.e. tumor counts), EPA used a linear model to calculate the benchmark dose (BMD). The Panel finds that the justification for using a linear model for multidose continuous data is insufficient and recommends that EPA provide further justification on the use of a linear model. The Panel further recommends that the modeling strategy for continuous data include polynomial models or nonlinear models (e.g., the Hill model) that are flexible enough to fit the data and would also adequately approximate a linear relationship.

Additionally, the Panel has the following comments and/or recommendations:

- The Panel agrees with EPA's derivation of RPFs from the BMDs (as opposed to the lower confidence limit of the BMDs), in order to accommodate comparison of studies with different precision. The Panel does not believe that any alternative approaches are necessary.
- The Panel recommends that when multiple doses are available for dose-response modeling, all the data should be used with a sufficiently flexible model, e.g., the multi-stage cancer model or a polynomial model for continuous endpoints.
- The Panel is concerned about using high-BMR values to calculate RPFs and recommends that the BMR be in the low-dose region.
- The Panel recommends that when single-dose studies are used to calculate the RPF, the impact on the RPF calculation should be described. [\[how would this be done?\]](#)

#### *Selection of PAHs for Inclusion in the Relative Potency Approach*

EPA describes the selection of PAHs for inclusion in the RPF approach. The Panel finds that the method for selecting the PAHs appears to be scientifically justified, but several issues such as individual study quality and study design variability across studies are incompletely

considered. The Panel recommends that a list of quality criteria be defined, articulated, and applied *a priori*, ~~prior~~ to the weight of the evidence evaluation. Only studies of sufficient quality should be considered in the weight-of-evidence evaluation. The Panel recommends that once a study is considered to ~~be of have~~ sufficient quality to be included, then differences in the variability of study design characteristics between studies be carefully considered prior to inclusion in the RPF calculation. [Is there a way that this can be practically accomplished? If so, it would be good to provide EPA with some guidance here.] Differences among studies in some of these design characteristics may significantly affect the dose-response within each study, which in turn, will affect the RPF calculation.

Additionally, the Panel has the following comments and/or recommendations:

- The Panel finds that the rationale for the omission of Ah-receptor data is well justified.
- The Panel agrees with EPA that once information on tumor formation is demonstrated, then the additional information on cytotoxicity and tumor promotion is not needed; however, the justification for omission of these data should be discussed.
- The Panel recommends using study quality as a means to include or exclude data, rather than statistical significance, and does not recommend using RPF detection limits for that purpose.
- The Panel recommends that the graphical arrays of the RPF calculations clearly identify the studies used to estimate the final RPFs, and recommends presenting the data as point estimates with information on variability as opposed to presenting the data as bar graphs.
- The Panel recommends integrating information provided in Appendix G into the narratives and presenting the narratives in a consistent structure, format, and order.

#### *Derivation of RPFs for Selected PAHs*

EPA describes various methods (e.g. prioritization of studies) and different averaging approaches for deriving final RPFs. The Panel has several reservations regarding the RPF calculation approach. The Panel is concerned about calculating RPFs based upon a single experiment as well as calculating RPFs using studies where there was only a single-dose level of BaP and/or the target PAH, particularly if it was a high dose. The Panel does not recommend calculating an RPF when only a single dose of the target PAH and only a single dose of BaP are available. An RPF can be calculated from only a single dose of BaP (if the tumor incidence is in the low-dose range) when adequate dose response data are available for the target PAH. The Agency is encouraged to continue evaluating other methods, such as using a geometric mean instead of an arithmetic mean. Using a geometric mean would give less weight to ~~outlier-extreme~~ values.

The Panel strongly believes that use of cancer bioassay data is essential for determining the RPF for a given PAH. Cancer-related endpoint data are useful as supporting data but the Panel does not recommend the use of only cancer-related endpoint data for determining the RPF. Therefore, the Panel does not recommend calculating an RPF for dibenz[a,c]anthracene and ~~recommends-suggests~~ that it be removed from Table 7.2 until further bioassay data become available.

Additionally, the Panel has the following comments and/or recommendations:

- The Panel does not recommend averaging RPF values from tumor incidence and tumor multiplicity data without sufficient justification for using the multiplicity data, and without adequate dose-response data for tumor multiplicity. In lieu of this, the Panel recommends that only tumor incidence data be used to calculate final RPFs.
- The Panel agrees with EPA's approach of averaging RPFs across all routes of exposure due to the lack of sufficient data. However, the Panel does not recommend calculating RPFs when the available data are only from non-physiological routes of exposure (i.e. lung implantation).
- The Panel generally finds that the scientific rationale presented in the document for the assignment of an RPF of zero, the assignment of no RPF, and the distinction between them is adequately described, but recommends that a consistent approach be adopted for using RPFs of zero. In addition, the Panel recommends the Agency discontinue assigning a value of zero to quality studies that have non-statistically significant results.
- The Panel agrees with EPA's characterization of the final RPFs with confidence ratings, but recommends that a measure of data quality be reflected in the ratings.

#### *Uncertainties and Limitations Associated with the RPF Approach*

EPA discusses the uncertainties and limitations associated with using the RPF approach for PAH mixtures ~~risk assessment~~. The Panel finds that the uncertainties in the methodology of deriving RPFs are well described. The major methodological uncertainties are clearly defined and discussed such that there is little doubt about the methods that were used and the limitations of the final RPF values reported. The Panel has the following recommendations to strengthen this section of the document:

- ~~Include Comparisons of~~ cancer risk estimates of complex mixtures using the RPF approach with results of actual and bioassay data, e.g. a reality check.
- Include a discussion on the relevance of high doses in animal studies to the much lower doses experienced by humans.
- Include a discussion on bioavailability.
- Include a discussion of the uncertainty that arises from the difficulty and limitation of completely characterizing mixtures.

#### *Adequacy of Appendices for Independent Verification*

The appendices in the document include dose-response data for potency calculations, benchmark dose modeling outputs, and calculation of RPFs to allow independent verification of the calculated RPFs. The Panel finds the appendices to be generally useful for verifying the calculations of the RPFs, but has the following recommendations:

Reorganize the appendices by chemical (with each identified in the Table of Contents). This would include the corresponding BaP data for each study within each chemical section which may be repeated across PAHs.

- Revise the plots from the BMD software output to be based on BMDs instead of the lower confidence limits of the BMDs (BMDLs).

### **Comments from Dr. Ingrid Burke**

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

All of the questions seem to be addressed.

In answer to the first charge question, regarding the overall scientific soundness of the RFP approach, the Panel writes that the scientific basis for the RFP approach is not well justified. This either needs a bit more elaboration here, or the answers to Charge Question 1 and Charge Question 2a should be merged.

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

Not that I can see.

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

The report is very interesting, particularly in its critique of the current methodologies and scientific basis for RFP. It is a VERY thorough report.

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

I believe so. However, I missed seeing statements about what the consequences of using the current methods are, such that one is left wondering what are the risks of using the current approach, relative to these criticisms. An additional statement for each recommendation could help clarify the importance of each, as it relates to current policy and consequences for the public.

## Comments from Dr. Thomas Burke

### General Comments

The review committee has done an in-depth evaluation of the Draft RPF document. However the findings, as presented present a mixed message. The Committee finds that the scientific basis for the approach is not well justified, but fails to make specific recommendations to clarify the justification and address this issue. At the same time the committee recognizes the “pragmatic need for the RPF approach”. This is a mixed message that needs to be clarified in the report.

The review addresses many gaps in our current understanding of mixtures that are not necessarily specific to PAHs. The issues of using only statistically significant studies, (p. 24 line 4 “using a cutoff P-value of .05 for inclusion of the data in the weight of evidence assessment is arbitrary”) the choice of linear model to calculate the BMD. (“The Panel finds that the justification for using a linear model for multidose continuous data is insufficient”). The many recommendations for further study need to be put in the broader context of the current limitations of our understanding of low dose interactions when assessing population risks.

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

The report lacks definitive “bottom line” conclusions in addressing the charge questions. For example, they conclude that the document is “logical, clear, and concise”. Yet in the next sentence they state that the approach is not “well justified”.

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

There do not appear to be any technical errors. However, there do appear to be instances where the committee recommends things that are not possible (and may not be possible for a long time) given the state of the science. Many times throughout the document the committee calls for more studies. The challenge is to present the best approach given the constraints of the current data.

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

Not as written. Is that overall conclusion that the approach is not scientifically justified?

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

A more concise statement of the major conclusions is necessary. Would the panel approve the application of this approach while the many additional studies they recommend are undertaken?

The report seems to be highly critical of the approach yet unclear about whether it is suitable for risk assessment in the absence of the development of the recommended whole mixtures approach.

## Comments from Dr. Terry Daniel

### General comments

The SAB review of the EPA's development of an RPF approach for PAH mixtures is thorough and clear. A number of useful suggestions are offered for improving the report, including modifications of the meta-analysis techniques for aggregating information over the relevant scientific literature and consideration of alternative models for determining RPFs and various slope and uncertainty parameters.

The argument that a different assessment method, based on PAH mixtures (or mixtures including PAHs, such as occur in coal tars, diesel and gasoline exhaust etc) seems very well-founded and certainly is consistent with the advice SAB has frequently given urging EPA to pursue multi-stressor, multi-media risk assessment science. However, in the current context this advice may present the Agency with something of a Catch 22. The EPA is under considerable pressure to update and codify risk assessment protocols to update risk criteria and standards that underlie important health-protection regulations. This review notes many of the short-comings of approaching the assessment of PAHs one at a time and urges work to develop more appropriate mixture-based approaches, but at the same time acknowledges that the science base for implementing a mixture approach is inadequate and likely to be that way for some time. The number of potentially environmentally relevant complex mixtures (of multiple PAHs, as well as PAHs with many other substances) is very large and not fully defined, and it would take considerable research effort and time to sort out the various mixtures that would most relevant and the nature of the multiple possible interactions among their various constituents. Acknowledging the difficulty, or even impossibility of actually using such a mixture approach at present, the review concludes that as a practical matter, the singular PAH RFP approach proposed in the EPA document is about the best that can be done. The impression, especially for persons not expert in the relevant science, is that EPA is using "bad science" to set regulations, but that has to be accepted as the best that they can do—giving little comfort to both the regulated and the protected. It would be better if the current approach (the best that can be done now) were reviewed as such (how well does the EPA do at implementing the best available approach) and the recommendation for initiating new science to support a better approach were more clearly distinguished and separated out as an important future effort.

### Quality Review Questions

1. YES: The original 9 charge questions and sub-questions to the SAB Ad Hoc Committee reviewing the EPA Development of a RPF Approach for PAH Mixtures were adequately addressed;
2. NO: There do not appear to be any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. YES: Committee's report is clear and logical;
4. YES: The conclusions drawn and the recommendations provided are supported by the body of the Committee's report.

### Some specific/editorial comments

Is the term “quantal data” standard for this field of science? Does it really mean “binary data” and is binary taken to be alternative to “continuous?”

The executing summary seems very long and overly detailed. For example specific lists of detailed recommendations are presented in the executive summary, while the main body of the review is more narrative and the specific recommendations are not listed.

P 10, line 9 needs a comma or two (“... key compounds, to BaP as ...” and perhaps ...single agent, and to real world ...”). In that same sentence, it seems that the **but** in “... cancer bioassay, but results ...” should be a **because**.

Somewhat separate from this particular review/quality review, the reference to the parallel review of the closely related a revision of the IRIS assessment of BaP raises the question of whether there should have been (or should be) some explicit coordination and cooperation in that effort and the current PAH effort—at least in the review processes.

The main body of the report notes (P 12) that “The document also discusses the role of the Ah receptor (AhR) in detail” and agrees with the EPA report conclusion that this is “not a good indicator ...” and thus recommends “removing this discussion and consideration of this mechanism.” In contrast, the executive summary (P 4) states “The Panel finds that the rationale for the omission of Ah-receptor data is well justified.”

In the discussion on P 14, where the committee suggests using a BaP-PAH1, PAH1-PAH2 strategy for expanding the number of studies that can be used to establish RPFs, the committee also cautions that “EPA should also take into account factors that could potentially outweigh the benefits in the establishment of a RPF for a specific PAH, such as cross-study and cross laboratory comparability issues.” Can the committee offer some specific examples for what these issues might be and how they might be addressed?

On P 32 the committee notes that the appendices are useful, but suggests that they be organized “by chemical.” Does this suggestion run counter to the approach of treating PAHs as a class with (assumed) similar MOA etc? It would seem that the suggested “by chemical” organization would make similarities and differences between chemical more difficult for the reader to find.

In the letter to the Administrator, “the Panel does not find the scientific basis for the RPF approach to be well justified in the document” seems a rather stark statement that could be misinterpreted. The statement is better qualified in the body of the document, where the judgment is parsed into 1) current deficiencies in the science needed to implement potentially better approaches (e.g., the whole mixtures approach) and 2) some short-comings in the EPA’s implementation of the single PAH RPF approach (e.g., suggested improvements in the meta-analysis techniques used, testing of alternative, non-linear models, alternative calculations of RPFs). Care should be taken in the letter not to imply that the EPA document is using “bad

science,” and to more clearly articulate how they could improve on their implementation of the “best available” science.

The letter does a better job than the report (especially the executive summary) of separating out the “whole mixtures” approach as a recommendation for new science initiative to improve future risk assessments, rather than a criticism of the use of science in the current RPF approach.

**Comments from Dr. George Daston**

1. Were the original charge questions adequately addressed?

I believe that the charge questions have been adequately addressed. I was especially pleased to see that the Committee supported the use of central tendencies for BMD to compare across PAHs. I believe this to be a better means of addressing mixtures, as it focuses more on the potencies of each mixture component rather than on the statistical power of the study on which the BMD was calculated.

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

I did not note any technical errors or omissions. I found the Committee's report to be thorough.

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

I found the report to be logically presented and easy to follow. There was good consistency between the body of the text, the Executive Summary and the cover letter. I felt that the cover letter touched on the most important elements of the review, which I think is more effective than reiterating every aspect of the review.

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

I believe that the Committee's report is extremely thorough and that its conclusions and recommendations are supported by the text.

I was a little disappointed that the recommendations emphasized additional studies and tumor data to validate the RPF approach. In this age of understanding of mechanisms of action and of 21<sup>st</sup> century approaches to toxicology, I would have much preferred a recommendation for an increased emphasis on mechanistic approaches, not on traditional tumor data.

## Comments from Dr. Costel Denson

### **Were the original charge questions to the SAB committee adequately addressed?**

Nine (9) charge questions were presented to the SAB committee for its review, with many of these consisting of a host of subsidiary questions. The committee addressed each of these questions adequately and in considerable detail, providing useful insight and recommendations in every case. In instances where the committee did not agree with the draft document, “Development of a Relative Potency Factor...” the committee explained why and suggested possible remedies.

### **Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the committee’s report?**

This reviewer could find no issue in the report that was not adequately considered and thought through.

### **Is the committee’s report clear and logical?**

The committee’s report is laid out in a clear and logical way. Each charge question is presented and discussed, and the associated recommendations are presented along with the particular question under consideration. However, this reviewer noted several instances throughout the report where the committee made the comment, “does not recommend”. We believe these statements to be a distraction, for they could dilute or reduce the strength of the actual recommendations. It is also possible that if the “not” is missed, the incorrect conclusion would be drawn.

### **Are the conclusions drawn or recommendations provided supported by the body of the committee’s report?**

There are roughly twenty-nine (29) recommendations presented in the report, and all appear to be supported by the body of the committee’s report.

**Comments from Dr. David A. Dzombak**

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

The charge questions appear to be adequately addressed.

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

I did not detect any technical errors or omissions, but I am not an expert in toxicology.

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

I believe that the organization of the report needs some revision. The charge questions are not made clear in the Executive Summary. Each charge question could be reduced to a key question for inclusion in the subsections of the Executive Summary.

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

The conclusions presented in the letter and in the Executive Summary appear to be supported by the body of the report.

**Comments from Dr. James K. Hammitt**

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

Yes, except the response to 1b is incomplete – what discussion is recommended and what material should be moved? (Part of the answer is on p. 28, which could be referenced.)

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

None that I am aware of.

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

Yes, with the following exceptions:

Response to question 1a, recommending new bioassays of mixtures, goes well beyond the charge question. Perhaps this material could go elsewhere, e.g., a section on panel recommendations.

pp. 17-18 are confusing. Is the panel reporting on EPA's analysis or conducting its own analysis?

p. 19, lines 7-8 are confusing. Would it be better to say "avoid comparisons that would require accounting for possible study-specific effects"?

p. 31, lines 5-7. What "additional information" on the relevance of high doses in animal studies to lower doses in humans should be added? This seems like a huge topic and some guidance on what the panel requests seems necessary.

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

Yes.

## **Comments from Dr. Bernd Kahn**

Concerning 'Development of a Relative RFP Approach..' EPA SAB Review, the answer is 'yes' to all four quality review questions. The report is well written. Here are some minor points:

p. ii, l. 19: This comment also refers to p. 1, l. 3, and to p. 13, l. 13: This belief can be clarified in the letter by using the words 'whole mixture approach' in the last sentence of this paragraph.

Recommending this approach is not made convincing elsewhere, at least to this reader who does not know if testing the cited 12 - 15 mixtures actually would be sufficient.

p. 9, l. 4: Is this emphatic comment reflected adequately in the letter and the Executive Summary?

Add a List of Acronyms.

**Comments from Dr. Agnes Kane**

## PAH Mixtures Document

The PAH Mixtures Review Panel has prepared a very insightful review that raises important fundamental concerns about the RPF approach. Toxicological evaluation of complex mixtures has not been adequately considered with respect to mechanism. This issue applied to PAHs is even more complicated since human exposures to PAHs frequently occur in combustion products where these chemicals are adsorbed onto solid particles as addressed on p.31. Future studies should incorporate solid particles (including nanoparticles) in developing a whole mixtures approach for these chemicals.

The remaining comments addressed the charge questions in detail and the report was succinct, clear, and logical. No technical errors or omissions were noted and the overall conclusions were well-supported in the report and supplemented by appropriate publications, especially the 2010 IARC Monograph.

## Comments from Dr. Madhu Khanna

1. Are the original charge questions to SAB adequately met?

The responses appear to fully address the charge questions. I have a few comments regarding clarity of the recommendations by the Review Panel

Specifically, Page 2, line 14-17- It would be helpful to elaborate a little more on how cancer bioassay data provides support for using the RPF approach. There isn't much information provided to support this even on page 10.

Page 3: In the following statement: "The Panel recommends that when single-dose studies are used to calculate the RPF, the impact on the RPF calculation should be described." It is not clear which impact is being referred to here and other than describing the impact if anything more can be said about how to evaluate it?

Page 5: line 11: In the following statement "In addition, the Panel recommends the Agency discontinue assigning a value of zero to quality studies that have non-statistically significant results." Can the panel suggest what value should be used in such cases and the justification for using a non-zero value? Also the report mentions that estimates with P-values higher than 0.05 should be considered if they are from a high quality study but does not say how large the P-value can be to consider the effect to be non-zero. Specific guidance on this matter might be useful for the EPA.

Page 20 line 6: As a non-expert in this area, it is not clear to me why BMR should be based on the low dose region and not the high dose region and how that is related to the shape of the dose response curves.

2. Any technical errors or omissions?

I am unable to discuss this since it is outside my field

3. Is the report clear and logical?

It appears to be clear and logical except for a few issues noted above

4. Are conclusions or recommendations supported by the body of text?

Conclusions and recommendations are supported by the text.

**Comments from Dr. Kai Lee**

I have reviewed the SAB document that reviews the EPA draft assessment on polycyclic aromatic hydrocarbons, and I support transmittal to the Administrator after the Board receives public comment. It should be noted that the SAB draft discusses matters beyond my own scientific knowledge and expertise.

The SAB review makes the significant comment that the scientific basis for the Relative Potency Factor (RPF) approach is not well justified. The committee summarizes the evidence available and the way that the RPF framework leads to inconsistencies when it is applied to that evidence. The committee makes a sensible case, but opines that the best practical course is to use the RPF approach for now anyway, while additional studies are carried out. Those studies would be aimed at finding better ways of analyzing the data.

This line of analysis makes a strong case that RPF should be doubted because its underlying assumption of additivity of the toxic effects of the components of PAH is not consistent the evidence. This conclusion seems similar to a Type I error.

I did not find what might be called a "Type II" error discussion in the review: how large an effect might there be, owing to interaction among PAH components, in light of the constraints provided by the evidence? An answer to that question would seem to be germane to the recommendation to continue using RPF. (It is possible that there is an answer to this question, which I missed because of my limited knowledge of toxicology.)

**Comments from Dr. Cecil Lue-Hing**

There were an unusually large number of charge questions - nine primary questions with sub-questions that made up a grand total of 27.

I believe that the charge questions were all adequately addressed.

I did not encounter any technical errors. However, this topic is outside my area of expertise.

The report appears clear and logical

The conclusions drawn are supported by the text of the Panel's report.

**Comments from Dr. L.D. McMullen**

I think the charge questions were answered for what I know of the topic.

## Comments from Dr. Judith Meyer

1. Were the original charge questions to SAB Committee adequately addressed?

YES

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

p. 11, lines 35-44: These seem like general statements, and it is not clear whether they are based on speculation or on published studies. If citations could be provided for these statements, the argument would be strengthened. This seems particularly relevant since later (p.12) the panel concludes that the RPF method is not well justified based on available data – but no citations to those available data have been provided.

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

Yes, although I have a couple suggestions for clarification.

a) I suspect most readers of this document will know what a “whole mixtures” approach is, but I don't (other than that one combines several PAHs and looks at their effect – in comparison to the effect estimated from a RPF approach?). A one sentence description of what is meant by this would make it more widely understandable. I also have no idea of what is meant by EPA's previous considerations of the whole mixtures approach (p. 13). Is there a document that could be cited to clarify what is meant by that?

b) p. 12, line 14: some specificity (i.e. citations) as to what literature reviews you are talking about would help.

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

YES

Minor editorial comments:

ES p. 3, lines 14-16: Parameterization of the model is mentioned in both of these sentences, and the second mention is redundant.

## Comments from Dr. James R. Mihelcic

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

The nine charge questions were adequately addressed.

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

I did not note any technical errors or omissions in the report.

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

The Science Advisory Board (SAB) Polycyclic Aromatic Hydrocarbon (PAH) Mixtures Review Panel's report is clear and logical. I have a few minor editorial comments that could make two sentences clearer.

- a) In the following sentence (Page 10, lines 5-9) should the Panel's report list the specific references to the "results" that call into question the second assumption.

"There are also results, some of which are discussed in the document, that call into question the second assumption – i.e., that there are no significant low-level interactions of PAHs in a mixture beyond simple additivity, and therefore that the effects (cancer risks) of a mixture of agents are the simple sum of the individual risks. "

- b) On page 14, lines 1-3, it is stated that the "The list of 74 PAHs provided in Table 2-1 is believed by the Panel to be reasonable in view of the criteria of having three or more fused rings and not containing heteroatoms, alkyl or nitro substituents." Later in the document it is stated that "The PAH Mixtures document is limited in focus to analyzing only unsubstituted PAHs with three or more fused aromatic hydrocarbon rings because they are the most widely studied members of the PAH chemical class"

I was wondering if the report can provide a short sentence that or edit the second sentence above regarding why 3 rings are used because the definition provided early in the document (page 7, lines 10-13) states "criteria of having three or more fused rings" came from as the WHO definition. As written, the total document implies that 2 ring PAHs are not widely studied members of the PAH chemical class.

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

The conclusions drawn appear supported by the Committee's report.

**Comments from Dr. Horace Moo-Young**

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

Yes. The Ad Hoc Committee adequately addressed the original charge questions.

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

There are no technical errors or omissions in the report.

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

The committee's report is clear and logical.

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

Yes, the conclusions and recommendations provided support the body of the report. The complex nature of PAH compounds in the environment requires that the agency strive to implement the panel's recommendation to test a portfolio of 12-15 different complex PAH mixtures, using animal bioassay studies. These complex PAH mixtures, should represent an assorted mixture, such as coal tars, creosote, and manufactured gas plant compounds that represents PAH compounds and mixtures of concern to EPA, and which most closely represent what can potentially occur in the field.

## **Comments from Dr. Duncan Patten**

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

The charge questions were adequately addressed including not only direct responses but also bulleted recommendations which added more detail.

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

This is outside my area of expertise and thus I can really comment on this question.

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

The panel's report is well organized and very clear, pointing out the strengths and weaknesses of the EPA ORD report.

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

As far as I can tell, the recommendations, which are basically the conclusions are based on sound science and the introductory commentary following each charge question.

## Comments from Dr. Amanda Rodewald

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

Overall, yes.

The following response seemed to need additional detail:

3.3. Charge Question 3 – Discussion of Previously Published RPF Approaches

18

19 *This chapter presents a discussion of previously published RPF approaches. Due to the*  
 20 *evolution of the state of the science and an increased understanding of PAH toxicology, EPA is*  
 21 *reevaluating the RPF approach for PAHs in this analysis.*

22

23 *3. Please comment on whether the discussion provides a meaningful background on how RPFs*  
 24 *have been derived in the past, and the advantages and disadvantages of previous methods.*

25

26 This chapter adequately summarizes the previous RPF approaches, but could be  
 27 improved by providing more quantitative information, and editing Table 3-1 to use a  
 28 standardized approach for reporting values (same significant figures, scale, etc.).

More detail about the type/amount of quantitative information would be useful.

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

No, other than the point mentioned above.

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

Yes. Please see comment below.

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

Yes.

#### *Other Comments:*

Page 1 of Executive Summary and page 8 response to charge question 1: The statements that there is no well justified scientific basis for the RPF approach (see below) sound strange to me without further explanation. That wording makes me question the entire approach. Is there a better way of wording those statements or subsequent ones to avoid the impression that the EPA is using approaches that clearly are without scientific support. The issue might be with the phrase "well justified". Does this mean that the scientific basis is believed to exist but is simply not articulated (i.e., the authors did not provide sufficient justification in the document), or that

the scientific basis is questionable (i.e., the available scientific data do not support the assumption)?

*Overall Scientific Soundness of the RPF Approach*

21 Overall, the Panel finds the document to be logical, clear, and concise. However, the  
22 Panel does not find the scientific basis for the RPF approach to be well justified in the document.

*36 Rationale for Recommending an RPF Approach*

38 EPA's document presents the scientific rationale for recommending an RPF approach for  
39 PAH mixtures. The Panel does not find the scientific basis for the proposed RPF approach to be  
40 well justified in the document.

*P8 response to charge question 1:*

9 Overall the Panel finds the PAH Mixtures document to be logical, clear, and concise.  
10 However, the Panel does not believe that the scientific basis for the RPF approach is well  
11 justified. Nevertheless, the Panel recognizes the pragmatic need for the RPF approach, and  
12 based upon the currently available data, recommends that EPA continue to use the RPF approach  
13 for PAH mixtures.

The committee articulated this issue somewhat on page 9 (see below), but the response was again phrased as "not well justified", leaving me unclear.

(23 At the face-to-face meeting, the Panel discussed this issue in considerable detail, and  
24 concluded that this charge question actually represents two distinct questions: **first whether,**  
**25 based on available literature, there is a sound scientific foundation for use of the single-agent**  
**26 relative potency factor (RPF) approach, particularly with respect to the two core assumptions of**  
**27 this rationale that were proposed in the PAH Mixtures document;** and second, whether there is a  
28 reasonable practical consideration in using the RPF approach at this time, independent of the  
29 scientific foundation and underlying assumptions.

**Comments from Dr. Jonathan M. Samet**

I have no specific comments on the PAH document and think that the four quality review issues have been appropriately handled.

## Comments from Dr. Kathleen Segerson

### 1. Are the charge questions adequately met?

Yes.

### 2. Are there any technical errors or omissions?

Not to my knowledge.

### 3. Is the report clear and logical?

In general, yes, although I note the following:

**Letter to the Administrator:** Some parts of the letter were not clear to me.

- It does not give a clear message regarding whether the RPF approach is scientifically sound or not. On page 1 of the letter, it states that “the Panel does not find the scientific basis for the RPF approach to be well justified in the document,” suggesting there is a sound scientific basis but the justification does not appear in the report. However, on p. 2 of the letter it suggests that EPA should collect more data so it can “potentially validate the RPF approach or potentially replace the RPF approach...” This language suggests that the approach might or might not be sound, and that it might need to be replaced. The letter should include a clearer statement about the Panel’s view on the scientific soundness of the approach.
- Related to the previous point, the letter states that the Panel “generally agrees with the EPA’s use of the RPF approach...”, while the executive summary (p. 1) states that the Panel “recommends that EPA continue to use the RPF approach.” The language in the executive summary seems somewhat stronger than the language in the letter. The same language should be used in both places to avoid any potential confusion or misinterpretation. I think that both this and the comment in the previous bullet could be addressed by including in the letter and executive summary the specific language that appears in the first full paragraph on p. 10 (“Despite these concerns.....could potentially replace it.”), which is much clearer (and stronger) on both points.
- P. 2 of the letter says “The Panel encourages the Agency to complete this document...”, suggesting that it reviewed an incomplete document. Should this read “finalize this document”, and, if so, is there some particular reason to urge that this document be finalized. Wouldn’t this be a generic statement for all EPA documents? Hence the intent of this language is unclear.
- P. 2 of the letter states that there is a critical need for an up-to-date cancer slope factor for BaP, and then goes on to say that “The Panel urges the Agency to quickly finalize the BaP assessment.” It is not clear from the letter what BaP assessment is being referred to here, since there is no previous reference to any BaP assessment in the letter. This would be clearer if it read something like “quickly finalize the BaP assessment that EPA’s is currently undertaking.”

**Executive Summary.** Some of the issues noted above about the letter apply to the executive summary as well. In addition, some of the recommendations included in the executive summary do not appear to be of sufficient importance to warrant inclusion in an executive summary (see, for example, the reference to editing Table 3-1 on p. 2, lines 28-29). In general, it seems that some distinction between “high level” and “low level” recommendations is needed. The executive summary should include high level recommendations but not low level ones. This would also shorten the executive summary, which seems to be a bit long and written almost as a litany of recommendations.

**4. Are the conclusions and recommendations supported by the body of the text?**

Yes. However, while the recommendations (or at least a subset of them) are bulleted in the executive summary, in the body of the report they are often buried in the text. In addition, as noted above, there is not a clear distinction between high-level and low-level recommendations. I think the report would be more effective if the major (high level) recommendations were somehow highlighted in the body of the report.

**Comments from Dr. James Sanders**

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

Yes. The Panel did a very good job of clearly addressing each charge question.

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

No. The report fully and accurately addresses the issues raised.

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

Yes. I have one minor suggestion. On page 1, I recommend deletion of the sentence in lines 39 and 40, because it repeats lines 21-22 on the same page.

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

Yes. The Panel's conclusions and recommendations are clear and appropriate.

## Comments from Dr. John Vena

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

The review committee systematically and thoroughly responded to each of the nine charge questions including each of the subsections subsumed under each of the leading charge questions. The narrative gives adequate background and rationale for the specific recommendations that follow to address the issues posed by each of the charge questions. The panel did a superb job in answering 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 Committee's report?

To my knowledge there were no technical errors or omissions in the report.

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

The narrative that provides the response to each of the charge questions is well-developed and carefully written. I found that the arguments across each of the charge questions were consistent logical and well presented. Most notably I found that when specific important points needed to be made the panel used tables, graphs and examples to back up the specific recommendations.

There were only a few instances where I thought the language could be improved and I found a few locations where specific editorial changes are recommended.

I believe that the in response to charge question one could be more clearly stated. The statement on page 8 line 10 "the panel does not believe that the scientific basis for the RPF approach is well justified" conveys to me the message that the RPF approach should not be pursued. Perhaps better wording here would be that

"The scientific basis of the impact of underlying assumption should be better described" or "the panel believes that "the scientific basis for the RPF approach could be justified more clearly."

Page 8 line 11 it would be helpful to clarify what is meant by "pragmatic need".

I believe that the key points on page 10 lines 18 through 20 and lines 30 through 32 should be incorporated into the cover letter and the executive summary.

Recommend edits to cover letter:

Pg 1 line 43 reword to read "the panel recommends that the scientific basis for the RPF approach could be justified more clearly." Add some of the language on page 10 lines 18-20; 30-32.

Pg1 Line 45 after assessing insert "carcinogenic risk from"

Pg 2 line 9 after BaP insert "IRIS"

Recommended edits to Executive summary:

Clarify the language on line 39

Page 2 line 4 clarify what is meant by pragmatic need

Page 3 line 34 define BMR

Page 6 line 4 define BMD

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

The panel made very clear and specific recommendations to improve the document. The recommendations were thorough and consistent.

## Comments from Dr. R. Thomas Zoeller

The following comments are provided in response to the 11/23/2010 memo by DFO Dr. Tom Armitage concerning the Quality Review of the SAB workgroup's document of the same date entitled, "*SAB Review of EPA's 'Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February 2010 Draft)'*". This memo asked contributing SAB members to specifically address the four quality review questions from the vantage point of our own expertise. These questions are:

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;
2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. whether the Committee's report is clear and logical; and
4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

Overall, the SAB document is thorough and well organized. The summary information at the beginning does a good job to abstract the main points made in the overall document. However, the concept that the SAB finds the RPF approach to lack scientific justification but that there is a pragmatic need is a very complex concept to articulate in the abstracted form. Perhaps there is a more accurate way to phrase this concept? Moreover, the document makes it clear that there are significant theoretical problems with this approach that will impact the data that will be derived from it. Therefore, it seems warranted to focus on the recommendation that the EPA base their analysis using a different approach?

**Quality Charge Question #1.** In general, the original charge questions to the SAB were adequately addressed. It may be more clear if these 9 questions were described earlier in the manuscript. The questions and refinements are recapitulated in the document, but having them stated at the beginning in sequence might allow the reader to see the scope of the SAB effort from the very beginning. Having said this, the material presented in the document is clear and thorough.

**Quality Charge Question #2.** This reviewer did not detect any overt technical errors or issues that were incompletely or inadequately addressed. It is not possible to determine fully whether omissions were made, but there were certainly no omissions relative to the original charge questions themselves.

**Quality Charge Question #3.** Overall, it seemed that the document make a very strong case for using an approach that differs from the RPF approach and even describes how this can be done. Therefore, it might be useful simply to state that?

**Quality Charge Question #4.** There are a series of recommendations made that are non trivial to carry out. These recommendations are well supported in the SAB review and clearly articulated. It seems clear that responding to these recommendations will considerably improve the EPA IRIS review for PAHs.