UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
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March 17, 2011

EPA-SAB-11-004

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: SAB Review of EPA's "Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February 2010 Draft)"

Dear Administrator Jackson:

EPA's current approach to assessing cancer risk for polycyclic aromatic hydrocarbon (PAH) mixtures uses the relative potency factor (RPF) approach, which estimates the cancer risk of individual PAHs relative to benzo[a]pyrene (BaP). In 1993, EPA published RPF values for 6 PAHs. EPA's Office of Research and Development (ORD) has updated the RPF values for these 6 PAHs and developed new RPF values for 18 additional PAHs, using recent studies from the published literature, as described in *Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February 2010 Draft).*

ORD requested the Science Advisory Board (SAB) to peer review the PAH Mixtures document, focusing on: rationale for recommending an RPF approach, discussion of 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 SAB convened the PAH Mixtures Review Panel to provide advice to the Agency. The key points and recommendations of the Panel are detailed in the report. Below is a brief highlight of the major comments and recommendations.

Overall, the SAB finds the document to be logical, clear, and concise. The SAB recognizes the pragmatic need for the RPF approach. Based upon the currently available data, the SAB supports EPA's use of the RPF approach for assessing carcinogenic risk from PAH mixtures. The SAB, however, provides recommendations to strengthen the scientific rationale for the RPF approach, the selection of studies, methods for dose-response modeling, and calculations of final RPFs.

Although the SAB supports the use of benzo[a]pyrene (BaP) as the index compound for the RPF approach, the cancer slope factor for BaP is outdated and it is essential that EPA expeditiously update the cancer slope factor for BaP.

The SAB also recommends that EPA consider developing a whole mixtures approach for PAHs. This approach could validate the RPF approach and in the future, could replace the RPF approach. 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 SAB recommends that the Agency seek support from the National Toxicology Program (NTP) and/or other entities to conduct testing of an appropriate portfolio of different complex PAH mixtures. These complex PAH mixtures should represent a diverse array of mixtures, but also represent the most important PAH mixture classes of concern to EPA.

We appreciate the opportunity to provide EPA with advice. We look forward to receiving the Agency's response.

Sincerely,

/Signed/

Dr. Deborah L. Swackhamer, Chair
EPA Science Advisory Board

/Signed/

Dr. Nancy K. Kim, Chair
SAB PAH Mixtures Review Panel

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Polycylic Aromatic Hydrocarbon (PAH) Mixtures Review Panel

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ACRONYMS

BaP	Benzo[a]pyrene
BMD	Benchmark Dose
BMDL	Benchmark Dose (Lower Confidence Limit)
BMR	Benchmark Response
CSF	Cancer Slope Factor
EPA	Environmental Protection Agency
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
NCEA	EPA's National Center for Environmental Assessment
ORD	EPA's Office of Research Development
PAH	Polycyclic Aromatic Hydrocarbon
RPF	Relative Potency Factor
SAB	Science Advisory Board

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

In 1993, EPA developed the document *Provisional Guidance for Quantitative Risk Assessment of PAH* that recommends a Relative Potency Factor (RPF) approach for assessing PAH mixtures. EPA's Office of Research and Development (ORD) has developed a draft technical document, *Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures,* hereafter called "PAH Mixtures document", to update the 1993 document by expanding the number of PAHs assessed and including recent studies from the published literature.

EPA's Office of Research and Development (ORD) requested that the Science Advisory Board (SAB) review the PAH Mixtures document. There were nine charge questions, which focused on the overall scientific soundness of the approach, on the specific chapters of the document, and the adequacy of the appendices to allow for independent verification. These charge questions are included in the Appendix and the responses to the charge questions are detailed in the report. The recommendations from the Panel for the major charge questions are highlighted below. Detailed responses to all the charge questions are presented in the body of the report.

General Comments

Overall, the Panel finds the document to be logical, clear, and concise. The Panel recognizes the pragmatic need for the RPF approach, and based upon the currently available data, recommends that EPA continue to use the RPF approach for assessing cancer risk for 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 more recent data in calculating and expanding the RPF values for PAHs. The Panel recommends that the Agency finalize the document based upon the Panel's comments and recommendations.

Rationale for Recommending an RPF Approach

EPA's document presents the scientific rationale for recommending an RPF approach for PAH mixtures. The Panel has several recommendations for strengthening the rationale for using the RPF approach. Additional historical perspective should be added, since it is an important component in, and justification for the agency's practical decision to continue with the RPF method. EPA indicated at the meeting that they had previously considered implementing a whole mixtures approach, but decided against it due to significant data gaps in available information. The Panel recommends including a discussion of these previous considerations and evaluation of data gaps, which would add to the rationale to continue with the RPF approach.

The Panel recommends strengthening the rationale by discussing that the RPF approach relies on a direct comparison between dose-response curves from actual cancer bioassay data between BaP as the index compound and the target PAH. 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 is aware that a revised Integrated Risk Information System (IRIS) assessment for BaP is under concurrent development, and urges the Agency to quickly finalize that assessment.

The Panel finds that EPA's assumption that interactions among PAH mixture components do not occur at low levels of environmental exposure is not well justified in the document; however, in the absence of data that support a specific interaction (additive, sub- or super-additive, etc.), a default assumption of additivity is reasonable for the purposes of the RPF analysis.

Concurrent with the continued use of the RPF approach, 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 future.

Discussion of Previously Published RPF Values

EPA presents a background on how RPFs have been derived in the past and a qualitative comparison between the previous RPF approaches and studies testing whole mixtures of PAHs. The Panel believes that the document adequately summarizes the previous RPF approaches, but could be improved by providing more quantitative information on the comparison between cancer risk estimates derived from the previous RPF approaches and those estimates derived from the whole mixtures approach. The Panel also recommends editing Table 3-1 to use a standardized approach for reporting values (same significant figures, scale, etc.).

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 animal bioassay data from studies of high quality may be dismissed. The Panel recommends that EPA consider exploring an approach where a 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 data from studies of high quality 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 used are derived from tumor incidence or multiplicity data.

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 multi-stage 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. 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 multi-dose continuous data is insufficient and recommends that EPA provide further justification on the use of a linear model. In addition, the Panel 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.

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 have sufficient quality, the variability in study design characteristics among studies be carefully considered prior to inclusion in the RPF calculation. 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.

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 with only a single-dose level of BaP and/or the target PAH, particularly if it was a high dose or if, only single doses of both the target PAH and BaP are available. The Panel does not make a recommendation on whether or not to calculate RPFs for PAHs with these data characteristics, recognizing that the Agency will need to apply professional judgment based on analyzing the actual available data. However, calculating an RPF from only a single dose of BaP is reasonable if the BaP tumor incidence is in the low-dose range and when adequate dose response data are available for the target PAH.

The Agency is encouraged to continue evaluating other methods for combining RPFs across studies, such as using a geometric mean instead of an arithmetic mean. Using a geometric mean would give less weight to outlier 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 that it be removed from Table 7.2 until further bioassay data become available.

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 so that little doubt remains about the methods that were used and the limitations of the final RPF values. 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 and bioassay data.
- 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).

2. INTRODUCTION

In 1993, EPA developed the document *Provisional Guidance for Quantitative Risk Assessment of PAH* that recommends a Relative Potency Factor (RPF) approach for assessing PAH mixtures. EPA's Office of Research and Development (ORD) has developed a draft technical document, *Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures* (February 2010 Draft), hereafter called "PAH Mixtures document", to update the 1993 document by expanding the number of PAHs assessed and including recent studies from the published literature.

PAHs are a class of chemicals that have variously been defined to include organic compounds containing either two or more, or three or more, fused rings made up of hydrogen and carbon atoms (WHO, 1998). The number of chemicals that comprise the PAH class is not known, but hundreds of PAHs are thought to be present in complex mixtures (WHO, 1998). PAHs do not occur in the environment as isolated entities; they primarily occur in complex mixtures generated from the incomplete combustion or pyrolysis of substances containing hydrocarbons. Some of the complex mixtures containing PAHs that are typically found in the environment include coal tar, manufactured gas plant (MGP) residues, coke oven emissions, diesel and gasoline exhaust, and coal plant emissions. Many PAHs are demonstrated to be carcinogenic in animal bioassays.

EPA's PAH Mixtures document presents a component-based approach to assessing the cancer risk of PAH mixtures by summing doses of component PAHs after scaling the doses relative to the potency of the selected index PAH, benzo[a]pyrene (BaP). The cancer risk is then estimated using the dose-response curve for the index PAH.

The PAH Mixtures document is limited in focus to analyzing only unsubstituted PAHs with three or more fused aromatic hydrocarbon rings. The analysis evaluated 74 PAHs, and final RPFs were calculated for 24 of the PAHs. Six of these PAHs have updated RPFs from the 1993 guidance, and 18 of these PAHs have new RPF values. Additionally, 3 PAHs were assigned an RPF of zero.

ORD has requested that the Science Advisory Board (SAB) conduct a review of the document. In response to ORD's request, the SAB Staff Office solicited nominations of experts and formed the SAB PAH Mixtures Review Panel. The Panel held a public teleconference on June 8, 2010, and a public meeting on June 21-23, 2010, to review EPA's Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures document and to deliberate over the charge questions. The Panel discussed its draft report during a subsequent conference call on September 30, 2010. The Panel's draft report was approved by the Chartered SAB on December 16, 2010, on a public teleconference call. There were nine charge questions, which focused on an overview of the document, on the specific chapters of the document, and the appendices. These charge questions are included in the Appendix and the responses to the charge questions are presented below.

3. RESPONSE TO EPA CHARGE QUESTIONS

The charge questions are presented below in italics, followed by the responses from the Panel in normal text.

3.1. Charge Question 1 – General Charge Questions

1a. Please comment on whether the report is logical, clear and concise. Please comment on whether EPA has clearly synthesized the scientific evidence for the derivation of relative potency factors for individual PAHs.

Overall the Panel finds the PAH Mixtures document to be logical, clear, and concise. EPA has clearly synthesized the scientific evidence for the derivation of relative potency factors for individual PAHs. The Panel recognizes the pragmatic need for the RPF approach. Based upon the currently available data, the Panel recommends that EPA continue to use the RPF approach for PAH mixtures. The Panel agrees with the Agency that in order to continue with the RPF method, it is important to expand the number of compounds in the 1993 guidance, and for the most part the candidate compounds for this expanded list are appropriate (see Chapter 4 discussion). The Panel also agrees that it is important to include more recent data for these compounds (since 1993) in calculating and expanding the RPF values for PAHs, since many of the values used in the current RPF method are based on older data.

1b. Please comment on whether the report provides adequate context for how the proposed RPF approach could be used in a PAH mixtures risk assessment.

The Panel finds that the PAH Mixtures document does not provide an adequate context for how the proposed RPF approach could be used in a PAH mixtures risk assessment. The Panel recommends that more discussion is needed to provide this context, including moving relevant portions from Chapter 7 (sections 7.3 and 7.4) into earlier sections of the document and providing an example (also see response to Charge Question 7e).

3.2. Charge Question 2 – Rationale for Recommending an RPF Approach

Chapter 2 presents the rationale for recommending an RPF approach. In an RPF approach, doses of component chemicals that act in a toxicologically similar manner are added together, after scaling the doses relative to the potency of an index chemical. Benzo[a]pyrene (B[a]P) is selected as the index compound for this RPF approach. The RPF approach involves two key assumptions related to the application of a dose-additivity model: (1) PAH components in the mixture act in a similar toxicological manner; and (2) interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment.

2a. Please comment on whether the report provides adequate justification for using an RPF approach as a scientifically defensible method to assess the cancer risk associated with exposure to PAH mixtures.

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

With regard to the first question, the Panel concludes that the rationale for the proposed RPF approach is not well justified in the current document. There are two basic assumptions that are proposed in the document as the basis for considering the RPF approach specifically for PAHs: first, that the chemicals of comparison are all assumed to act in a similar toxicological manner as the reference compound (i.e., benzo[a]pyrene - BaP); and second, that their effects are additive by assuming no significant interactions at low, environmentally relevant doses.

The Panel considered the PAH Mixtures document, the studies cited within, as well as other data. The document discusses studies that call into question both of the underlying core assumptions and further elaborates on a number of other uncertainties, some of which cannot currently be validated or dismissed, that further undermine the logical basis for the assumptions on which the RPF method is based. These are discussed in more detail in response to charge questions 2c and 2d below, but are briefly summarized here. It is not clear that the first assumption – i.e., that the other PAHs under consideration act in a similar toxicological manner as BaP - is required as a foundation for the RPF method, since for these particular PAHs the method is based on the outcomes of cancer bioassays, rather than the underlying toxicological action. There are also results, some of which are discussed in the document (page 23, lines 11-19; page 39, lines 3-12 and Table 2-2), 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.

Despite these concerns about the underlying justification for the RPF method and the logic of the two core assumptions, the Panel concludes that there is adequate practical justification for continuing to use this approach in the near term to assess cancer risk of PAH mixtures in the absence of a good alternative. In particular, although this Panel and previous expert panels have strongly suggested that the EPA move toward a whole mixtures-based approach, the fact remains that the regulatory and scientific communities do not have sufficient information to adopt a whole mixtures approach for risk assessment at this time. Therefore, the Panel recommends the continued use of the component-based RPF approach as the most practical choice but recommends that this should proceed in parallel with continued development of one or more whole mixtures-based approaches that could potentially validate the RPF approach or possibly replace it.

Given these conclusions, the Panel has several recommendations for revising the document and moving forward with the RPF approach. First, additional historical perspective should be included in the revised document, since it is an important component in, and justification for the agency's practical decision to continue with the RPF method. EPA indicated that they had previously considered implementing a whole mixtures approach, but decided against it due to data gaps in available information. The Panel recommends including a discussion of these previous considerations and evaluation of the data gaps. This would help with the rationale for continuing with the RPF approach.

In parallel with the continued use of the RPF approach, the Panel recommends that EPA begin developing a whole mixtures approach to achieve two goals: (1) to potentially validate the RPF approach, and (2) to explore as a possible replacement for the RPF approach in the near future. The Panel recommends that the Agency set these goals as strategic initiatives, with specific timelines and benchmarks. This would lay the foundation for an underlying concerted research program to achieve these goals.

The Agency should seek support from the National Toxicology Program (NTP) or other entities to test a portfolio of 12-15 different complex mixtures in animal studies. These mixtures should represent a diverse array of mixtures but also represent the most important mixture classes of concern to EPA (based on the level of health concerns and/or extent of exposure) such as coal tar, manufactured gas plant (MGP) residues, coke oven emissions, diesel and gasoline exhaust, coal plant emissions, etc. With these data in hand, one could then potentially validate the RPF approach and also compare an environmental mixture to this portfolio of standardized mixtures and be able to adequately estimate risk.

These mixtures could also be compared to a surrogate mixture (e.g., a mixture representing the ca. two dozen compounds being assessed in the RPF method) as well as BaP as a single agent. This would provide a direct validation of the RPF method and link these results to previous data on environmental samples for which RPF compound values are known.

2b. Please comment on whether the choice of benzo[a]pyrene as the index compound is scientifically justified and appropriately described. Please identify and provide the rationale for any alternative index compound(s) that should be considered.

The choice of BaP as the index compound is well justified and is appropriately described for this RPF approach. It is the best studied PAH and meets the criteria for an index compound for an RPF assessment. The Agency noted that a revised IRIS assessment of BaP is undergoing a parallel review that will likely lead to a revised cancer slope factor (CSF) as well as separate values for oral, dermal and inhalation BaP exposures. An up-to-date estimate of the CSF for BaP is central to the validity of the RPF method since this is the index compound, and the Panel urges the Agency to quickly finalize the BaP assessment.

2c. Please comment on whether the weight of evidence indicating that PAHs, as a chemical class, have a similar mode of carcinogenic action has been adequately described and is scientifically justified.

There is some evidence that a subset of closely related PAHs have a similar mode of action in inducing cancer as described in the document. This is not unexpected since the compounds in question have already been defined in large part by their comparison to BaP. However, although these compounds have similar modes of action, available data indicate that they each act via different precise mechanisms when examined at a more detailed level. For example, even though many PAHs are metabolized to reactive intermediates that then form DNA adducts at guanine residues, their potency for conversion of DNA adducts to mutations varies among compounds. Moreover, the pattern of guanine mutations within specific DNA sequences varies among these adducts. By definition, these adducts are therefore acting by slightly different mechanisms. Since cancer risk can be related to mutation rate and to specific mutations within certain DNA sequences, this will result in different risks even though these compounds share a similar mode of action.

Additionally, there are hundreds of other PAHs and PACs that may not act by these modes of action and that likely, particularly in complex mixtures, contribute in positive or negative ways to the overall carcinogenicity of the mixture. These compounds should also be considered in the RPF method if adequate cancer bioassay data are available.

Also of importance, other PAHs in a mixture may alter the risk for known PAHs in that mixture in more complicated ways. For example, through mass action a complex mixture may contain total PAHs that collectively overwhelm the levels of an individual PAH such as BaP, perhaps by 1000:1 or greater. These may collectively interfere with the overall metabolism of BaP, or ratios of specific metabolites, or the capacity to repair DNA adducts from BaP, etc., such that one cannot predict the cancer risk from BaP solely from its concentration in the mixture. Therefore, this assumption is not well justified.

In addition, there is a question as to whether similar modes of action are sufficient to predict *in vivo* carcinogenicity. As discussed in the PAH Mixtures document (e.g., page 35, section 2.6), mutagenicity, genotoxicity and similar short-term assays are relatively poor predictors of in vivo carcinogenesis. Yet a basic assumption of the document is that this information is sufficient to predict their relative carcinogenicity. There are PAHs that are positive in short-term in vitro assays but negative or weak in animal bioassays, and vice versa, further undercutting this basic assumption.

The document also discusses the role of the Ah receptor (AhR) in detail as another potential unifying mode of action for carcinogenic PAHs. However, elsewhere in the document, EPA also acknowledges that interaction with and activation of the AhR is not a good indicator of promotion or in vivo tumorigenesis for PAHs (as opposed to dioxins). The Panel agrees with this latter assessment.

Taken together, these points argue that there are weaknesses in using the assumption of PAHs having a similar mode of action as a rationale for using the RPF approach. The Panel

recommends strengthening the rationale by including a discussion about the RPF approach relying on a direct comparison between dose-response curves from actual cancer bioassay data between BaP and the target PAH.

2d. Please comment on whether the assumption that interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment has been adequately described and is scientifically justified.

The assumption that there are not significant interactions among PAHs in complex mixtures at low doses is not well justified in the document. As discussed in the document (page 23, lines 11-19) coal tar behaved differently in *in vivo* carcinogenesis assays than would be predicted from studies with BaP as a single agent, or what would likely be predicted from a RPF approach based on BaP as the index chemical. Likewise, as discussed in the document (page 39, lines 3-12 and Table 2-2), the complex and unpredictable results to date of simple binary combinations of PAHs that do not follow simple additivity also undercuts the assumption of interactions between PAHs not occurring at low environmental levels. However, in the absence of consistent data that support a specific type of interaction (additive, sub- or super-additive, etc.) that could be used for a variety of PAH mixtures, a default assumption of additivity is a reasonable assumption for the purposes of the RPF analysis.

It should be noted, however, that complex mixtures such as coal tar, MGP residues, creosote, diesel exhaust and other PAH mixtures contain hundreds of other compounds, not included in this RPF assessment, that likely contribute to the overall biological effects of the mixtures. Other contributing mechanisms may include: induction or suppression of specific metabolic pathways; competition for metabolism through mass action at active sites; epigenetic effects; promotion and progression effects; endocrine disruption, and neurological and immunological effects that contribute to cancer risk. Other classes of potentially potent carcinogens including substituted PAHs, volatile organic compounds (VOCs), metals, as well as other compounds may also be present. Collectively, these mechanisms and compounds may contribute in complicated ways to the overall cancer risk of a complex mixture. This uncertainty can be reduced by directly testing mixtures in cancer bioassays. As discussed above the Panel recommends the Agency test 12-15 complex mixtures of concern to EPA.

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

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

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

This chapter provides a summary of previous RPF approaches and provides a qualitative discussion and comparison of cancer risk estimates based on RPF approaches with estimates obtained from testing whole mixtures. The Panel finds that this chapter adequately summarizes

the previous RPF approaches, but could be improved by providing more quantitative information on the comparison between the previous RPF approaches and the whole mixtures approach. The Panel also recommends editing Table 3-1 to use a standardized approach for reporting values (same significant figures, scale, etc.).

3.4. Charge Question 4 – Evaluation of the Carcinogenicity of Individual PAHs

This chapter discusses the development of a database of primary literature on PAH carcinogenicity and cancer-related endpoints and the criteria used to include or exclude studies from the database.

4a. Please comment on whether the list of 74 PAHs (Table 2-1) included in the initial literature search is complete. Please comment on whether the rationale for the choice of PAHs included in the literature search has been appropriately described. Please identify other databases or resources that should be included.

Chapter 4 of the PAH Mixtures document details the basis for the selection criteria that was used to develop the database related to PAH carcinogenicity and cancer-related endpoints. 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. The development of the database of primary literature on PAH carcinogenicity and cancer-related endpoints and the criteria used to include or exclude studies from the database are described in detail within this chapter. The database appears adequate, with the recommendation that a recently published IARC Monograph on PAHs, Volume 92, be included as an additional resource (IARC, 2010).

4b. Chapter 4 includes a description of how studies were selected for use in dose-response assessment. Please comment on whether the choices and assumptions in making the selection have been adequately described. Please comment on whether the information in Tables 4-1 through 4-14 provides adequate information to inform how decisions were made. Please comment on whether studies were rejected or included appropriately. Please comment on whether positive and nonpositive studies have been considered appropriately.

The basis for selecting which studies were used in dose-response assessment is clearly delineated. The information in Tables 4-1 through 4-14 provides adequate information related to whether certain studies were rejected or included in this document. However, the criteria for including or rejecting a study should be revised to include only studies that are deemed to be of sufficient quality using *a priori* standards as described in the response to charge question 6a. Given this revision of including only studies of high quality, the EPA approach inappropriately discards data that do not achieve statistical significance. Please see the response to charge question 6a for further detail.

4c. The methodology for the choice of studies to use in the derivation of RPFs includes studies where at least one PAH was tested at the same time as B[a]P. Studies where individual PAHs were tested without concurrent testing of B[a]P were not included in the quantification of RPFs. Please comment on the scientific rationale for this approach. Please comment on whether the advantages and disadvantages of excluding certain data from the derivation of RPFs have been adequately described.

Chapter 4 of the document stipulates that BaP had to be tested concurrently to include a study on the carcinogenicity or other cancer-related endpoints of one or more of these 74 PAHs. This restriction raises a concern that data from carcinogenicity studies of high quality might be dismissed. The Panel recommends that EPA consider whether a PAH other than BaP, with a RPF that has a comparatively narrow range, might be able to serve as the surrogate for the BaP index compound in those instances where BaP was not included in a bioassay. This approach offers the possibility that additional data from studies of high quality could be included in the development of a RPF for a given PAH. The Panel recommends that this be examined especially in those instances where limited animal bioassay data were used to establish a RPF value. 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 has a few recommendations that relate to the evaluation of the carcinogenicity studies for individual PAHs. These recommendations include providing some quality assessment to individual studies, such as a tabulation for various studies, including information on: 1) sample size, 2) dosing, 3) mortality (prior to tumor development), 4) defined test compound purity, and 5) whether or not the data used are tumor incidence or multiplicity data.

In addition, the Panel recommends incorporating or reiterating some of the discussion about alternatives for ranking RPFs provided in Appendix G into the discussions on individual PAHs in Chapter 4 as well as in Chapter 6. For example, the Panel considers the discussion about the influence of the route of administration on the RPF calculations to be particularly informative.

3.5. Charge Question 5 – Methods for Dose-Response Assessment and RPF Calculation

This chapter describes the selection of dose-response data and methods for dose-response assessment and RPF calculation from the selected datasets. The methodology for estimation of the RPFs varied depending on the characteristics of the datasets, however, the general equation was the ratio of the slope of the dose-response curve for the subject PAH to the slope of the dose-response curve for B[a]P.

5a. Please comment on whether the scientific rationale for the dose-response modeling approaches used in the derivation of RPFs is adequately described. Please comment on whether there are other appropriate modeling approaches for estimating the relative potencies of PAHs. Please describe alternative approaches (e.g., other model forms) that could be considered.

The Panel finds that the scientific rationale for the dose-modeling approaches is adequately described. The panel does have recommendations on additional modeling approaches that could be considered. The modeling approaches described in Chapter 5 of this document for multi-dose studies are based on whether the data are quantal (binary) or continuous. The quantal endpoints considered in this document include tumor incidence or incidence of cancer-related endpoints, including frequency of mutations per number of cells interrogated. The continuous endpoints include tumor counts (number of tumors per animal) or cancer-related endpoints of a continuous-variable nature (e.g., number of sister chromatid exchanges, number of morphologically transformed colonies).

When modeling quantal data, the mean model is for the probability of response (e.g., tumor incidence) and is generally assumed to follow a sigmoid-shape. Commonly used models that could be used include the logistic, probit, multi-stage, and Gompertz models. Since the multi-stage cancer model has a biological basis, it is the standard model used for cancer incidence and is considered sufficiently flexible to accommodate the dose-response data for these PAHs. Specifically, the multi-stage cancer model for the probability of a tumor is parameterized based on the number of dose groups (g) with the polynomial assumed to equal g-2:

$$\mu = \beta_0 + (1-\beta_0)\left[1-\exp(\beta_1 x + \beta_2 x^2 + ... + \beta_{g-2} x^{g-2}\right].$$

It should be noted that a model for data with g dose groups will exactly track the sample means (here, sample proportions) if the degree of the polynomial is g-1. However, a variation of this general model, typically used in risk assessment, assumes a monotonic relationship and constrains all parameters to be non-negative. The Benchmark Dose (BMD) Software used in the document makes such an assumption as the default analysis. With quantal data, assumed to be independent across and within-dose groups, it is generally assumed that the data are binomially distributed with binomial variance (i.e., with n subjects evaluated at a dose group, the variance in the number "responding" is assumed to be $n\mu(1-\mu)$). Alternatively, the data may follow hyper- or hypo-binomial variability, i.e., greater than or less than binomial variability. These assumptions are not specified in the document and should be. The BMD Software used to estimate unknown model parameters uses a maximum likelihood estimation criterion and standard iterative algorithms for estimation. However, these distributional assumptions and the parameterization of the multi-stage cancer model should be clearly stated in the document. It is not clear whether the assumption of binomial variability was verified; the assumption of binomial variability should be verified and the document should include information about the verification. Instead, the model checking was based on the goodness-of-fit of the mean model and did not assess the assumptions regarding variability.

For continuous endpoints, a nonlinear dose-response shape may be expected from the data. However, the analysis plan for continuous endpoints is to use a linear model (i.e., a linear function). The justification for using the linear model for the multi-dose continuous data is

insufficient and additional justification should be added. Although the linear model is the simplest model, there are other models such as the Hill model or polynomial model that are commonly used. EPA's justification for using the linear model is that there are a small number of dose groups. This is an inadequate explanation.

The modeling strategy for the continuous endpoints should 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. In some cases, the variance in response is assumed to be constant over the dose range of observed data. A least-squares (or nonlinear least squares) criterion is used to estimate unknown model parameters. In contrast, the sample variance may change with the mean. For example, the responses in the low-dose region may have lower variance than that observed as the dose (and response) increase. Such data may be estimated using a quasi-likelihood estimation criterion.

For the continuous data included in this document, the assumption about whether the variance changes across the dose groups is not addressed and the potential for a nonlinear shape is not allowed. Only a linear model was used to estimate the mean response. A goodness-of-fit criterion was used; if the model did not provide adequate fit, high-dose groups were sequentially eliminated in an effort to achieve adequate fit. This strategy is arbitrary and should be avoided. A more flexible model should be used instead that accommodates the nonlinearity of the data.

Selection of Benchmark Response (BMR)

Since the RPFs are going to be used to estimate cancer risks at generally low environmental exposures, the calculation of RPFs should be applicable to the low-dose range, preferably excess risks ≤ 0.10 for quantal data. Similarly for continuous data, the calculation of RPFs should preferably be based on changes in the mean of less than or equal to one standard deviation (and certainly less than two standard deviations) in order to remain in the low-dose region of interest. For normally-distributed data, a change in the mean from the control mean of two standard deviations will result in approximately 50% of the subjects in the abnormal range. The RPF can increase or decrease substantially as dose (incidence or response) changes.

The analysis strategy described in Chapter 5 (with the suggested changes included) should be specifically followed. Deviations from the planned analysis strategy should be clearly explained.

To illustrate the use of a nonlinear model, the *in vitro* clastogenicity dose-response data of Tong et al (1981) (Table C-19, page C-85 of PAH Mixtures document) is reanalyzed. For convenience, the data table is reproduced in Table 1. The data clearly follow a nonlinear relationship, which is particularly evident, considering the two highest concentrations of benz[a]anthracene (BaA) that have similar responses with a log change in concentration.

Table 1: Data from Tong et al, 1981, for sister chromatid exchange summary data (Record number: 21710; Table C-19, page C-85). The BMR was set to the control mean from the predicted Hill model + SD of the control group. The BMDs are estimated from the Hill model using the specified BMR.

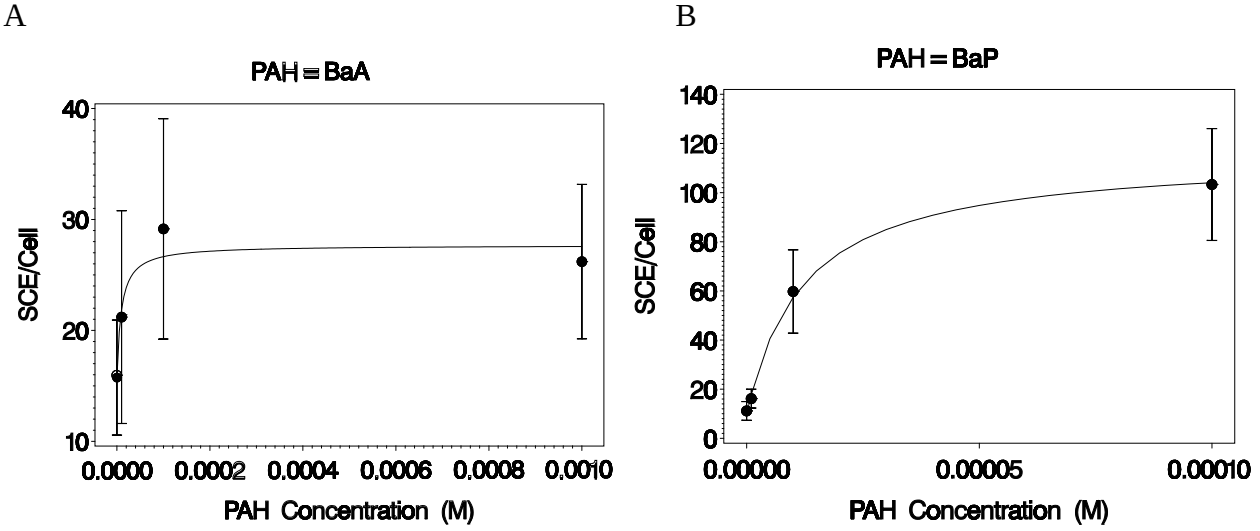
PAH	Concentration (Molar)	Mean Sister Chromatid Exchange/cell	Standard Deviation (SD)	Benchmark Response (BMR)	Benchmark Dose (BMD) (Molar)
Control	0	11.15	3.81	13.7	4×10^{-7}
BaP	10^{-6}	16.15	3.83		
BaP	10^{-5}	59.75	16.96		
BaP	10^{-4}	103.3	22.75		
Control	0	15.75	5.18	20.9	7×10^{-6}
BaA	10^{-5}	21.2	9.59		
BaA	10^{-4}	29.15	9.93		
BaA	10^{-3}	26.2	6.96		

Instead of fitting a linear model to these data, a 3-parameter Hill model is selected, which can accommodate an asymptotic response for large concentrations, i.e.,

$$\mu = \alpha + \frac{\gamma x}{x + \theta},$$

where x is the concentration of the PAH, α is the response for the control group, γ is the range of response such that $\alpha+\gamma$ is the asymptote for large x. Since only sample means and standard deviations are available at each concentration level, a weighted analysis is imposed, with weights set to the inverse of the sample standard deviation at each concentration. Unknown parameters are estimated using a weighted least squares criterion in a Gauss-Newton iterative algorithm using PROC NLIN in SAS (version 9.2). The resulting predicted models for BaP and BaA are provided in Figure 1. Using all of the data, a Hill model adequately fits the observed sample means for both PAHs.

Figure 1: Observed sample means and predicted response from a Hill model. Sample means are denoted with dots and +/- one standard deviation from each mean is denoted by the error bars.



The specified BMR for continuous data is one standard deviation (SD) above the control mean as predicted from the Hill model (shown in Table 1). For BaP, the estimated BMD_{1SD} is 4×10^{-7} and for BaA, the estimate is 7×10^{-6}. However, in Table E-14 (page E-31), the BMR and BMD values are blank and the point estimate responses are 92 and 13 for BaP and BaA, respectively; and the point estimate dose is $1x10^{-4}$ for both compounds. It is not clear how the point estimate responses were calculated. This is an example where the described analysis plan does not seem to be followed without any explanation of why it was not followed.

5b. For each individual dataset considered in the assessment, the B[a]P dose-response was calculated from the study-specific data. Please comment on whether this approach has been appropriately described. If there are additional approaches using the available data that should be considered, please describe how the approach could lead to a better estimate of cancer risk.

The strategy of using study-specific data for the BaP dose-response with PAH dose-response is advantageous since downstream calculations are intra-study and avoid comparisons that would require accounting for possible study-specific effects. This strategy has been appropriately described and the Panel does not have other approaches to suggest.

It should be noted that the estimates of BaP slope across studies with different characteristics are very different. The range of the estimates can be more than 1,000 fold. This supports the idea of using study-specific estimates for calculating the RPFs.

5c. The point of departure for slope estimation that has been used for the derivation of RPFs is the benchmark dose (BMD) estimate rather than the lower confidence limit on the benchmark dose (BMDL). Please comment on whether this approach is scientifically justified and adequately described. Please comment on whether alternative approaches should be considered.

It is correct to base the derivation of the RPFs on the estimate derived from the BMD, rather than the lower confidence limit on the benchmark dose (BMDL), in order to obtain an estimate of the total exposure for a mixture (expressed as the total BaP equivalent dose). Due to chance experimental variation, some of the RPFs will be overestimated and some will be underestimated. These biases will tend to cancel each other for the total exposure of a mixture. On the other hand, when the study sizes are similar, the BMDLs between the BaP and PAH may be stable. But when the two studies have different precision, the ratio of BMDLs is tenuous. Therefore, the ratio of BMDs is advisable. The Panel does not believe that any alternative approaches are necessary.

5d. Please comment on the methodology used for the RPF calculations for multidose and single dose datasets. Please comment on whether the process for calculating RPFs from the various datasets is scientifically justified and adequately described. Please comment on the utilization of high response levels in some instances as the point of comparison. Please describe alternative approaches that could lead to a better estimate of cancer risk that should be considered using the available data. Please comment on whether the considerations for RPF calculation as outlined in Sections 5.6 and 5.7 are scientifically justified and adequately described.

When multiple doses are available for dose-response modeling, all of the data should be used with a sufficiently flexible model, e.g., the multi-stage cancer model or a polynomial model for continuous endpoints. An example of such an analysis strategy is given in 5a above. In the Appendix, there are cases where single-dose data were used when multiple doses were available; this should be explained.

Generally, the Panel is concerned about using high-BMR values to calculate the RPFs in single-dose studies. If the dose-response curves were parallel across PAHs, then the choice of BMR would not impact the estimation of a relative potency factor. However, as discussed in earlier chapters, it is generally assumed that the chemicals are not dilutions of one another, so their dose-response curves will generally not be parallel. Thus, the choice of the BMR should be in the low dose-region. However, in some special cases, the RPF calculation is not dependent on the response level. For example, consider the data from a BaP single-dose study and multi-dose comparison PAH for benzo[k]fluoranthene (BkF) (LaVoie et al, 1982). For convenience, the data from Table C-1, page C-4 of the PAH Mixtures document are reproduced below in Table 2.

Table 2: Data from LaVoie et al, 1982 for dermal bioassay data (Record number: 630; Table C-1, page C-4) – primarily squamous cell papilloma in female mice. The data include a single-dose study for BaP and multiple-dose study for the PAH, BkF.

PAH	Dose (μg/mouse)	Number of Animals in Group	Number of Animals with Tumors	% Tumor-bearing animals
Control	0	20	0	0
BaP	30	20	17	85
BkF	30	20	1	5
BkF	100	20	5	25
BkF	1000	20	15	75

Suppose a one-stage model is used for analysis of the single-point BaP study, i.e.,

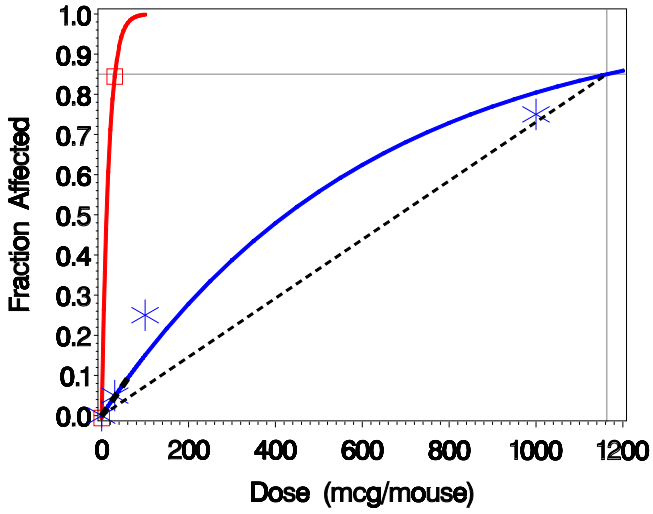
$$\mu = \beta_0 + (1-\beta_0)\left[1-\exp(-\beta_1 x)\right]$$

where β_0 =0, x is the dose of BaP, and β_1 is the unknown parameter associated with the slope. Assuming a zero background response rate (i.e., β_0 =0), the BMD(10) is estimated as $BMD(10) = -\log(0.9)/\beta_1$ and the BMD(85) is estimated as $BMD(85) = -\log(0.15)/\beta_1$. Since there are four dose groups for BkF, a multi-stage model is used, parameterized with linear and quadratic terms (i.e., g-2= 2 for a second-degree model):

$$\mu = \beta_0 + (1-\beta_0)\left[1-\exp(-\beta_1 x - \beta_2 x^2)\right]$$

where x is the dose of BkF and again we assume β_0 =0. However, in the EPA document, β_2 was set to zero and the one-stage model was used due to convergence problems. Therefore the same parameterization is used for both BaP and BkF. The fitted dose-response curves are provided in Figure 2. Notice the predicted response from the single-dose study is the sample mean (here, observed sample proportion).

Figure 2: Single-dose data for BaP (red) and multi-dose data for BkF (LaVoie et al, 1982).



When the one-stage model is used for both chemicals, the choice of BMR is not relevant in the calculation of the RPF. Consider the following algebraic manipulations to demonstrate for a general BMR=μ_0 and for a general j^{th} PAH:

$$RPF = \frac{\mu_0 / BMD(\mu_0)_j}{\mu_0 / BMD(\mu_0)_{BaP}} = \frac{BMD(\mu_0)_{BaP}}{BMD(\mu_0)_j}$$
$$= \frac{-\log(1-\mu_0)/\beta_{BaP}}{-\log(1-\mu_0)/\beta_j}$$
$$= \frac{\beta_j}{\beta_{BaP}}$$

Thus, the RPF is not a function of the BMR when a one-stage model is used for both the BaP and comparison PAH. To illustrate from the LaVoie (1982) data, the results for a BMR of 10% and 85% (the observed response from BaP) are given in Table 3. The resulting RPFs are identical.

Table 3: Illustration with BaP single dose study and multi-dose comparison PAH, here BkF from LaVoie et al, 1982.

LaVoie et al 1982 data	BMD10 estimates (μg)	Slope = 0.1/BMD10	BMD85 estimates (μg)	Slope = 0.85/BMD85
BaP	1.7	0.060	30	0.028
BkF	64.6	0.0015	1163	0.0007
RPF = $\frac{\text{slope PAH}}{\text{slope BaP}}$		0.025		0.025

This illustration demonstrates that in a single-dose study, a one-stage model can be fit, which will exactly predict the observed mean response. In this case, the ratio of slopes for calculating the RPF is not dependent on the BMR. However, with the single-dose studies, there is no way to verify the prediction where data are not available. Therefore the result is based on a lack of information rather than evidence that both the BaP and PAH dose-response data are adequately approximated with one-stage models.

Although the use of single-dose study data may be helpful in informing the risk assessment, these studies are clearly less informative than multi-dose studies. When single-dose studies are used to calculate the RPF, the Panel recommends describing the impact on the RPF calculation. For example, in Table 7-1, the Panel recommends including the number of studies per RPF calculation based on a one-dose study.

For section 5.7 of the document, the Panel recommends the use of a (g-1)-degree polynomial in the multi-stage model (page 111, lines 31-36) instead of reducing the degree of the polynomial. This model will exactly track the observed sample means.

3.6. Charge Question 6 – Selection of PAHs for Inclusion in the Relative Potency Approach

This chapter describes the selection of PAHs for inclusion in the RPF approach. The evaluation focuses on whether the available data were adequate to assess the carcinogenic potential of each compound. If the data were not considered adequate, then the PAH was excluded.

6a. Please comment on whether the rationale for the weight-of-evidence evaluation is scientifically justified and adequately described. Please comment on whether the approach adequately considers the available information. Please comment on whether other information (e.g., additional structure-activity) could contribute further to the weight-of-evidence evaluation and how this information could be utilized in the analysis.

The Panel believes that the method for selecting the PAH appears to be scientifically justified, but has recommendations about several issues that are incompletely considered. These

issues include: (1) the quality of the individual studies considered and (2) the variability of other design characteristics among studies, and how this may weigh on their evaluation prior to inclusion in the weight-of-evidence evaluation or calculation of an RPF.

Regarding the quality of individual studies being considered, the Panel recommends that a list of quality criteria should be defined, articulated, and applied *a priori* (e.g., methodologically robust, such as inclusion of an adequate control group, sample size, dose level, number of doses, number of PAHs measured, purity of the compounds considered, etc.) prior to the weight-of-evidence evaluation. This information should be illustrated in the form of tables or individual graphs. Only studies of sufficient quality, as defined *a priori*, should be considered in the weight-of-evidence evaluation.

The Panel recommends that once a study is considered to have sufficient quality, the variability of other study characteristics among studies should be carefully considered prior to their use in the calculation of the RPF. Some of these study characteristics include: species, strain and sex of animal model, route of exposure, form of exposure (injection, implantation, etc.), frequency of administration, exposure duration, location of tumors, types of tumors (papillomas, adenomas, carcinomas etc.), and stage of tumors (benign, malignant). Differences among studies in some of these characteristics may significantly affect the dose-response within each study, which in turn, will affect the RPF calculation. For example, for a given PAH one may have one study that used skin tumorigenesis and another that used implantation of solid material intratracheally. The latter study, if positive, might add weight to the overall determination that the PAH is tumorigenic in animals, but may be a poor study from which to calculate dose-response or relative potency. Or one could be comparing one study that has a physiological exposure route such as inhalation, ingestion, or dermal application, with one with a non-physiological exposure such as an intraperitoneal or implantation study. Likewise, there are tumor models, such as the A/J mouse, where tumor multiplicity counting is required due to the high penetrance of tumor response. It is not a simple task to reconcile these studies with other studies of tumor incidence for the purposes of quantitatively assessing dose-response.

There is no simple formulaic method for determining, *a priori*, how to include or exclude such studies or how to weight them, since this will vary depending on the individual PAH and also depending on what studies are available; it also requires a measure of expert scientific judgment. Instead, the Agency should clearly articulate the quality criteria (e.g., expand and articulate the characteristics listed in Table 7.1), and then only use studies with adequate quality to calculate RPFs. Weighting factors may be required for inclusion of some studies for RPF calculations, or they may only be valuable as a qualitative, weight-of-evidence assessment of carcinogenicity rather than for quantitative RPF calculations. The criteria for how such decisions are made for each study and each PAH should be clearly defined and described by the Agency as part of its assessment.

The EPA approach inappropriately discards data that do not achieve statistical significance. Lack of statistical significance does not necessarily mean that an effect is zero. It could be that there is an effect with biological relevance, but the sample sizes were too small to achieve statistical significance. Using a cutoff P-value of 0.05 for inclusion of data in the weight-of-evidence assessment is arbitrary. It can create a scenario where there are two studies

of equally high quality and one study is included because it has a P-value = 0.04 and the other study is not included because it has a P-value = 0.06. A study of high quality that produces a low statistically non-significant RPF is relevant and must be included in calculating the best (weighted average) estimate for an RPF. Discarding values in the lower tail of a statistical distribution, solely due to lack of statistical significance, results in a biased estimate of the effect.

6b. The weight-of-evidence analysis does not include data related to Ah-receptor binding, cytotoxicity or tumor promotion. Please comment on whether the scientific rationale for this decision is appropriate. If these data should be considered in the derivation of RPFs, please describe how they should be incorporated into the analysis.

The Panel finds that the rationale for omission of Ah-receptor data is well justified. Additional information is not necessary. The Panel also agrees with EPA's decision that once information demonstrating tumor formation is obtained, additional information on cytotoxicity and tumor promotion is not necessary. However, the document should clearly state the reasons for the omission of these data.

6c. The analysis uses an RPF detection limit as a means of comparing positive and nonpositive (or negative) bioassays. Please comment on whether this method is scientifically justified and adequately described.

EPA employed the use of an "RPF detection limit" to evaluate the results of positive and nonpositive results in the same test system. The "RPF detection limit" was defined as the RPF determined by the lowest response that would have been statistically significant for the subject PAH and the actual benzo[a]pyrene response. The Panel did not find this definition to be clear nor did the Panel find the description of the use of "RPF detection limits" to be clear. The Panel does not recommend utilizing statistical significance as a means to determine which studies to include or exclude. As discussed above, the Panel recommends assessing study quality to determine which studies to include or exclude from the weight-of-evidence evaluation. It is scientifically incorrect to discard data of sufficient high quality that do not achieve statistical significance and therefore, the Panel does not recommend using "RPF detection limits" for that purpose.

6d. Graphic arrays of the calculated RPFs (Figures 6-2 through 6-35) are presented as a means of representing the variability in RPFs from different data sources, the weight-of-evidence for carcinogenic potential, and the basis for the selected RPF. Please comment on whether the figures are informative and adequately described. Please comment on whether there is other information that should be included in the figures. Please comment on whether the narratives are informative and complete.

The Panel finds that Figures 6-2 through 6-35 provide a good summary of the individual studies considered and the variability of individual RPF estimates across studies. However, the Panel recommends clearly indicating which studies were used to estimate the final RPF. This would make the figures much more informative.

With respect to the presentation of RPFs for individual studies, the Panel proposes that rather than graphically displaying the RPF for each individual study as a bar, it can be shown as a point estimate coupled with information on variability (e.g., standard error, standard deviation, confidence interval, and range). The information on variability in the study is viewed as key, to help the reader interpret the study findings.

The Panel recommends that, for ease of reading and to ensure completeness, the narratives be presented in a consistent structure and format, both in terms of the information presented, as well as the order in which they are presented. The Panel also recommends integrating information provided in Appendix G into the narratives that correspond to Figures 6-2 through 6-35.

3.7. Charge Question 7 – Derivation of RPFs for Selected PAHs

This chapter describes various methods (e.g. prioritization of studies) and different approaches for deriving final RPFs (e.g., arithmetic mean). Final RPFs were derived by averaging the individual study RPFs (across all exposure routes) calculated from bioassay data for PAHs that had at least one RPF based on a bioassay. The exception was dibenz[a,c]anthracene, where the RPF was calculated from cancer-related endpoint data.

7a. Please comment on the scientific justification for the approach for deriving the final RPFs and the discussion of alternative options for the estimation of the final RPFs. Please comment on the reporting of the range of RPFs as a measure of variability instead of a confidence interval. Please comment on whether the data are adequate to support more (or less) precision in deriving the RPFs.

The Panel believes that presenting the range instead of a confidence interval is appropriate. The Panel does have reservations regarding several aspects of the RPF calculation approach. First, the Panel has concerns regarding calculating RPFs based upon a single experiment (e.g., 11H-benz[b,c]aceanthrylene, benzo[g,h,i]perylene, benzo[e]aceanthrylene, benz[j]aceanthrylene, dibenzo[a,h]pyrene, indeno[1,2,3-c,d]pyrene and naphtho[2,3-e]pyrene). Second, there is concern regarding the use of data for calculating RPF values in which there was only a single-dose level of BaP and/or the target PAH being evaluated (e.g., benz[a]anthracene, 11H-benz[b,c]aceanthrylene, benzo[e]aceanthrylene, naphtho[2,3-e]pyrene and fluoranthene), particularly if it was a high dose, and/or particularly if only single doses of both the target PAH and BaP are available. An RPF can be calculated from only a single dose of BaP when dose response data are available for the PAH. Since the RPF varies with the level of the tumor incidence, RPFs should only be calculated from a single dose of BaP if the tumor incidence at the dose of BaP is in the low-dose range; certainly, only if the BaP tumor incidence is less than 50%. Finally, there is concern about calculating the arithmetic mean for PAHs that have markedly divergent individual RPFs (e.g., benzo[c]fluorene). The Panel does not make a recommendation on whether or not to calculate RPFs for PAHs with these data characteristics, recognizing that the Agency will need to apply professional judgment based on analyzing the actual available data.

The Agency is encouraged to continue evaluating other methods, such as using a geometric mean instead of an arithmetic mean. Where sufficient data are available, the use of a geometric mean would give less weight to outlier values. Further, examination of the variability for estimates of RPFs in several of the figures indicates that a log-normal distribution may be appropriate to describe the variability of RPFs. Hence, the geometric mean would be a better estimate of central tendency. Also, the best central estimate would be a weighted geometric mean where the weights are inversely proportional to the square of the standard errors. That is, RPFs with large standard errors would receive less weight. The Panel believes that calculating RPFs to one significant figure is appropriate.

7b. Please comment on whether the scientific rationale for consideration of bioassay data versus cancer-related endpoint data has been adequately described. Please comment on whether the cancer-related endpoint data could be used in a more quantitative manner. Please comment on the justification of the final RPF derived for dibenz[a,c]anthracene. Please comment on the use of tumor multiplicity data in the weight-of-evidence evaluations and for the determination of the RPFs.

The Panel believes that the scientific rationale for considering bioassay data versus cancer-related endpoint data has been adequately described. The Panel strongly believes that the 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. As such, the Panel does not have recommendations on how to use cancer-related endpoint data in a more quantitative manner. The Panel does not recommend calculating an RPF for dibenz[a,c]anthracene and recommends that it be removed from Table 7.2 until further bioassay data become available.

The Panel recommends that additional information and justification be provided for the inclusion or exclusion of cancer bioassay data for PAHs that did not give significant tumor responses in well-designed studies. One suggestion is to include the IARC classification for those PAHs where a classification exists in Table 7.1 or perhaps in Table 7.3. The Panel believes that there is a need for some additional measure of the quality of individual studies used in determining the final RPF values. This is important in addition to the confidence ratings provided in Table 7.3 (see also further discussion below). The Panel also strongly believes that more cancer bioassay data with mixtures would be extremely helpful in further validating the RPF approach.

Tumor multiplicity (continuous data; average number of tumors per mouse) and tumor incidence (quantal data; percentage of mice with tumors) represent different measures of tumorgenicity/carcinogenicity. In the document, RPFs calculated from tumor multiplicity data are combined with other RPFs calculated from tumor incidence data to calculate final RPFs. An example of the problem is benzo[c]fluorene. The divergent RPFs used to calculate the final RPF value for benzo[c]fluorene in Table 7.1 come from averaging a study where multiplicity data were used (RPF of 50) and one where incidence data were used (RPF of 1). It is recommended that RPF values not be averaged from these two different measures without sufficient justification for using the multiplicity data. In this regard, accurate assessment of differences in potency using tumor multiplicity requires adequate dose-response data. For accurate

comparisons, at least 3 doses of each PAH should be available for comparison. In addition, these doses should be distributed across the dose-response range and not be clustered on the high or low end of the dose response range. In lieu of adequate dose-response data for tumor multiplicity, the Panel recommends that only tumor incidence data be used to calculate final RPFs. Additionally, if calculated RPFs for a given PAH still remain divergent across multiple well-designed studies due to multiple factors (e.g., combining incidence and multiplicity, combining data from different organs, combining data from different routes of exposure, etc) the Agency may wish to consider use of the geometric mean in place of the arithmetic mean as discussed above.

7c. Please comment on whether the recommendation to apply the proposed RPFs across all routes of exposure is adequately described. Please comment on whether there is additional scientific information that would inform this recommendation. Please comment on whether the available data are adequate to recommend exposure route-or target organ-specific RPFs.

The Panel finds that the recommendation to apply the proposed RPFs across all routes of exposure is adequately described. The Panel does not believe that there would be much value in providing route- or target organ-specific RPFs at the present time because a significant proportion of the studies used to calculate the final RPFs involved dermal application/carcinogenesis (approximately 60% of the studies involve dermal application to mice and >90% of the studies were conducted in mice). Additional studies and data using different routes of exposure and tumor data from other organ sites would be necessary to calculate such RPFs. Although the Panel agrees with the decision to not calculate separate RPF values for different routes of exposure, the route of exposure may be an issue of concern for generating RPF values for compounds where the available data are only via non-physiological routes (e.g., benzo[g,h,i]perylene, lung implantation in rat only; benzo[j]aceanthrylene, intra-peritoneal only; fluoranthrene, intra-peritoneal only; indeno[1,2,3-e]pyrene, lung inplantation in rat only). Additional dermal or oral tumor studies may be warranted in these cases since the route of exposure can play an important role in bioavailability and toxicokinetics that may alter the relative potency of the test compound as compared to BaP, when tested via a more standard route of exposure. A sensitivity analysis should be performed to determine, in those cases where there are data from several routes of exposure, whether these alternative routes cause a particular bias or greater variability in the RPF values. It is interesting to note in this regard, that some compounds, such as benzo[c]fluorene, demonstrate widely divergent RPFs in studies using different routes of exposure (in this case, oral versus interperitoneal, with values of 1 and 50) (see also dibenz[a,h]anthracene and dibenzo[a,l]pyrene). Without additional supporting data or justification, the Panel does not recommend developing RPFs for compounds with data only from studies using non-physiological routes of exposure.

7d. Please comment on whether the scientific rationale for the assignment of an RPF of zero for some PAHs is adequately described. Please comment on whether there are other data that should be considered to assess whether an RPF of zero is appropriate. Please comment on whether the scientific rationale for assigning no RPF based on inadequate data for some PAHs is adequately described. Please comment on whether there are alternative methods for assigning RPFs to these PAHs. Please comment on whether the text provides adequate distinction between PAHs with RPFs of zero and PAHs with no selected RPF and whether this distinction is useful for describing uncertainty in determining the cancer risk associated with PAH exposure.

The Panel generally believes that the scientific rationale presented in the document for assignment of an RPF of zero, the assignment of no RPF, and the distinction between them is adequately described. However, the Panel does have concern regarding the quality of the data used to assign an RPF of zero for some studies and also regarding the inconsistent use of studies with RPFs of zero in calculating the final RPFs. The Panel recommends that a consistent approach be adopted for using RPFs of zero for all compounds for which final RPFs are calculated. In addition, the Panel recommends that the Agency continue to evaluate how RPFs of zero are calculated as well as the rationale for assigning no selected RPF values. In addition, the Panel recommends the Agency discontinue assigning a value of zero to studies of high quality that have non-statistically significant results. See the response to charge question 6a for further details. The Panel did not identify alternative methods for assigning RPFs to PAHs that had inadequate data.

7e. The final RPFs are characterized with confidence ratings. Please comment on whether the rationale for the confidence ratings is appropriately described. Please comment on whether there are other approaches for describing confidence using the available data that could be applied in either a qualitative or quantitative manner that would be more useful for risk assessment.

In general, the Panel believes that characterizing the final RPFs with confidence ratings is a good idea and finds that the rationale for confidence ratings is appropriately described. However, the confidence ratings do not appear to give any indication of the overall quality of the data being assessed and used for the RPF calculation. Based on the information provided in Table 7.3, confidence ratings appear to be related to the number of studies used, data from more than one route of exposure, presence of non-cancer endpoint supporting data to calculate the RPFs, etc. The Panel strongly believes that there needs to be some measure of the quality of the individual studies used to generate the RPFs. In this context, quality refers to study characteristics, such as sample size and statistical power, presence or absence of non-lethal toxicity, unusual mortality, and other potential confounding factors. Also, the Panel's comments and recommendations in the response to Charge Question 7c may be useful in developing confidence ratings.

Chapter 7 also includes a description of how the RPF method is used to calculate relative cancer risk from exposure to PAH mixtures (section 7.3). In addition, there is a section (section 7.4) dealing with the use of age-dependent adjustment factors (ADAFs) to adjust for differences in susceptibility during early life (i.e., <16 years of age). The Panel believes that these two sections are extremely important to the overall presentation of the document and are somehow lost by inclusion at the end of Chapter 7. It is strongly recommended that the information on

cancer risk assessment (sections 7.3 and 7.4) be moved to the beginning of the document as a separate section.

3.8. Charge Question 8 – Uncertainties and Limitations Associated with the RPF Approach

This chapter discusses the uncertainties and limitations associated with using the RPF approach for PAH mixtures risk assessment. Many of the general uncertainties related to chemical-specific risk assessment are also applicable to the proposed RPF approach for PAHs. In addition, uncertainties exist regarding the selection of data and dose-response assessment methodology, the selection of PAHs for inclusion in the analysis, the derivation of the final RPF, the assumption of a common mode of action and dose additivity, and the extrapolation of RPFs across exposure routes.

8. Please comment on whether, overall, the document describes the uncertainties and limitations in the methodology used to derive RPFs in a transparent manner. Please comment on whether the most important uncertainties and limitations are identified. Please comment on whether there is existing information that could be used to evaluate the accuracy or validity of the RPF values to predict the cancer risk associated with exposure to PAH mixtures.

The uncertainties in the methodology of deriving RPFs are described quite well in the PAH Mixtures document. The major methodological uncertainties are clearly defined and discussed so that there is little doubt about the methods that were used and the limitations of the final RPF values reported.

More data dealing with the comparisons of the RPF approach and estimates of cancer risk derived from complex mixtures are needed, which would reduce some of the uncertainties associated with the RPF approach described in the document. The feasibility of directly studying complex mixtures is illustrated by the limited pair of existing data sets. Chronic bioassays in mice for two synthesized coal tar mixtures were conducted at the National Center for Toxicological Research, Food and Drug Administration (Culp et al., 1998). The RPF approach applied to these data were reported in the Electric Power Research Institute (EPRI) public comments (Rohr, 2010). Comparisons of cancer risk observed in the chronic animal bioassays for the two coal tar mixtures were within a factor of two to four (lower) of the cancer risks based on the RPF approach. This is an encouraging result for use of the RPF approach, albeit for only two mixtures. Additional comparisons, such as those submitted by EPRI, should be added to the document as it provides very useful information about the RPF approach. Statistical variation of cancer risk estimates between chronic animal bioassays on the order of three to four is expected (Gaylor et al., 2000). More data dealing with the comparisons of the RPF approach and estimates of cancer from tested mixtures are needed.

Additional mixtures of PAHs need to be studied in chronic animal bioassays in order to compare the observed cancer risk of a mixture with the risk estimated from the RPF approach. Section 3.1 of the PAH Mixtures document discusses the availability of several studies on mixtures that provide data for comparing cancer risk estimates using the RPF approach with

direct estimates of risk from the mixtures. Unfortunately, no quantitative information was presented in the document to indicate the potential size of uncertainty for the RPF approach. This quantitative information needs to be added to the document in order to evaluate the accuracy and precision of the RPF approach from existing examples.

The cancer slope factor for BaP is multiplied by the RPFs in order to obtain cancer unit risk factors for each of the PAHs. Hence, the cancer unit risk factor for BaP is critical to the calculation of the cancer risk estimate for a mixture using the RPF approach. Based on old studies, the upper limit of the cancer unit risk factor for lifetime oral exposure to BaP is 7.3×10^{-3} per μg/ kg per day listed in the EPA Integrated Risk Information System (IRIS), 1994. Based on a Good Laboratory Practice (GLP) study the upper limit of the cancer unit risk factor for BaP is 1.2×10^{-3} per μg/kg per day (Gaylor et al., 2000). Because of the relatively large uncertainty in the cancer unit risk factor for BaP, this value needs to be updated before reliable estimates of cancer risk can be derived for mixtures of PAHs.

Extending the classes of PAH should be considered by incorporating other PAH derivatives, e.g., PACs that occur in mixtures, particularly where bioassays exist such as for nitro-aromatics and alkylated PAHs.

The relevance of high doses in animal studies to the much lower doses experienced by humans is not discussed in the document. The Panel recommends that additional information or discussion of the uncertainty that arises from extrapolating from high animal doses to low human doses be added to the document.

The state of a single PAH administered to animals in bioassays may be different from the state of the same PAHs in mixtures where they may not be easily desorbed from solid particles. The bioavailability to humans for PAHs in a mixture needs to be compared to the bioavailability in animal bioassay experiments that utilize purified PAH compounds. Cancer risk estimates based on the RPF values and the total concentration of PAH in mixtures may be overestimated.

Using measured concentrations of PAHs in mixtures, sensitivity analyses can indicate which uncertainties in individual RPFs have a significant impact on the total BaP equivalents for a mixture. EPA should consider adding this to the document, perhaps by using the mixtures discussed in the EPRI comments.

The composition for each individual mixture must be adequately determined, otherwise uncertainty is added to the RPF approach. Completely characterizing mixtures is difficult, and this limitation and uncertainty should be discussed. For example, different PAHs may have different effects on the induction phase I and/or phase II enzymes that might affect the metabolic activation or deactivation of other potentially highly tumorigenic PAHs, i.e., a non-additive effect as mentioned in the PAH Mixtures document. Various PAHs may inhibit each other. Mixtures may or may not contain substances that act as promoters of tumorigenesis rather than as genotoxic initiators. Without adequately characterizing mixtures, these effects may not be considered.

3.9. Charge Question 9 – Adequacy of Appendices for Independent Verification

9. Please comment on whether the information in the Appendices is adequate to allow independent verification of the calculated RPFs. If not, please comment on what additional information would be useful.

There are 7 appendices in the document and the information contained in them include: a bibliography of secondary sources reviewed for identification of primary literature, a bibliography of studies without BaP as a reference compound, dose-response data for potency calculations, benchmark dose modeling outputs, calculation of RPFs, an example calculation of an RPF detection limit, and evaluation of alternatives for ranking RPFs.

The appendices are generally useful for verifying the calculations of the RPFs. However, the Panel recommends reorganizing 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.

The plots from the Benchmark Dose Software output are useful but it should be noted that the linear extrapolation to the origin is based on BMDLs instead of BMDs. The calculation of the multi-stage cancer slope factor is also given based on the BMDL instead of the BMD. The Panel recommends that the slope factors be added to these appendices based on the BMD – which is the approach taken in the document.

4. REFERENCES

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APPENDIX – EPA CHARGE QUESTIONS

National Center of Environmental Assessment Charge to External Reviewers for the *Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures* for the IRIS Program
February 2010

U.S. EPA's IRIS Program is seeking an external peer review of the scientific basis supporting the document titled *Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures* that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is a human health assessment program that evaluates quantitative and qualitative risk information on effects that may result from exposure to specific chemical substances found in the environment. Through the IRIS Program, EPA provides quality science-based human health assessments to support the Agency's regulatory activities. Combined with specific exposure information, government and private entities use IRIS to help characterize public health risks of chemical substances in site-specific situations in support of risk management decisions.

PAHs do not occur in the environment as isolated entities; they primarily occur in complex mixtures generated from the incomplete combustion or pyrolysis of substances containing carbon and hydrogen. Many PAHs are demonstrated tumorigenic agents in animal bioassays and are active in cancer–related *in vivo* or *in vitro* tests. In addition, PAHs exhibit noncancer effects that may be of concern to public health. The analysis presented in the document under review represents an RPF approach for estimating cancer risk and is characterized as one approach to assessing cancer risk from exposure to PAH mixtures.

In concordance with U.S. EPA (2000, 1986) guidance for health risk assessment of chemical mixtures, assessment of the cancer risk from human exposure to a particular PAH mixture would best be conducted with quantitative information on the dose-response relationship for the mixture of concern. When data for the mixture of concern are not available, the recommendation is to use toxicity data on a sufficiently similar mixture. However, quantitative cancer dose-response information exists only for a few complex PAH-containing mixtures. Component-based approaches, involving an analysis of the toxicity of components of the mixture, are recommended when appropriate toxicity data on a complex mixture of concern, or on a sufficiently similar mixture, are unavailable. The RPF analysis under review is not a reassessment of individual PAH carcinogenicity, but rather provides an approach for estimating cancer risk for PAH mixtures by summing doses of component PAHs after scaling the doses (with RPFs) relative to the potency of an index PAH (i.e., benzo[a]pyrene). The cancer risk is then estimated using the dose-response curve for the index PAH.

Below is a set of charge questions that address general and scientific issues in the document. Please provide detailed explanations for responses to the charge questions.

General Charge Questions

1a. Please comment on whether the report is logical, clear and concise. Please comment on whether EPA has clearly synthesized the scientific evidence for the derivation of relative potency factors for individual PAHs.

1b. Please comment on whether the report provides adequate context for how the proposed RPF approach could be used in a PAH mixtures risk assessment.

Chapter 2. Rationale for Recommending an RPF Approach

Chapter 2 presents the rationale for recommending an RPF approach. In an RPF approach, doses of component chemicals that act in a toxicologically similar manner are added together, after scaling the doses relative to the potency of an index chemical. Benzo[a]pyrene (B[a]P) is selected as the index compound for this RPF approach. The RPF approach involves two key assumptions related to the application of a dose-additivity model: (1) PAH components in the mixture act in a similar toxicological manner; and (2) interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment.

2a. Please comment on whether the report provides adequate justification for using an RPF approach as a scientifically defensible method to assess the cancer risk associated with exposure to PAH mixtures.

2b Please comment on whether the choice of benzo[a]pyrene as the index compound is scientifically justified and appropriately described. Please identify and provide the rationale for any alternative index compound(s) that should be considered.

2c. Please comment on whether the weight of evidence indicating that PAHs, as a chemical class, have a similar mode of carcinogenic action has been adequately described and is scientifically justified.

2d. Please comment on whether the assumption that interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment has been adequately described and is scientifically justified.

Chapter 3. Discussion of Previously Published RPF Approaches

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

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

Chapter 4. Evaluation of the Carcinogenicity of Individual PAHs

This chapter discusses the development of a database of primary literature on PAH carcinogenicity and cancer-related endpoints and the criteria used to include or exclude studies from the database.

4a. Please comment on whether the list of 74 PAHs (Table 2-1) included in the initial literature search is complete. Please comment on whether the rationale for the choice of PAHs included in the literature search has been appropriately described. Please identify other databases or resources that should be included.

4b. Chapter 4 includes a description of how studies were selected for use in dose-response assessment. Please comment on whether the choices and assumptions in making the selection have been adequately described. Please comment on whether the information in Tables 4-1 through 4-14 provides adequate information to inform how decisions were made. Please comment on whether studies were rejected or included appropriately. Please comment on whether positive and nonpositive studies have been considered appropriately.

4c. The methodology for the choice of studies to use in the derivation of RPFs includes studies where at least one PAH was tested at the same time as B[a]P. Studies where individual PAHs were tested without concurrent testing of B[a]P were not included in the quantification of RPFs. Please comment on the scientific rationale for this approach. Please comment on whether the advantages and disadvantages of excluding certain data from the derivation of RPFs have been adequately described.

Chapter 5: Methods for Dose Response Assessment and RPF Calculation

This chapter describes the selection of dose-response data and methods for dose-response assessment and RPF calculation from the selected datasets. The methodology for estimation of the RPFs varied depending on the characteristics of the datasets, however, the general equation was the ratio of the slope of the dose-response curve for the subject PAH to the slope of the dose-response curve for B[a]P.

5a. Please comment on whether the scientific rationale for the dose-response modeling approaches used in the derivation of RPFs is adequately described. Please comment on whether there are other appropriate modeling approaches for estimating the relative potencies of PAHs. Please describe alternative approaches (e.g., other model forms) that could be considered.

5b. For each individual dataset considered in the assessment, the B[a]P dose-response was calculated from the study-specific data. Please comment on whether this approach has been appropriately described. If there are additional approaches using the available data that should be considered, please describe how the approach could lead to a better estimate of cancer risk.

5c. The point of departure for slope estimation that has been used for the derivation of RPFs is the benchmark dose (BMD) estimate rather than the lower confidence limit on the benchmark dose (BMDL). Please comment on whether this approach is scientifically justified and adequately described. Please comment on whether alternative approaches should be considered.

5d. Please comment on the methodology used for the RPF calculations for multidose and single dose datasets. Please comment on whether the process for calculating RPFs from the various

datasets is scientifically justified and adequately described. Please comment on the utilization of high response levels in some instances as the point of comparison. Please describe alternative approaches that could lead to a better estimate of cancer risk that should be considered using the available data. Please comment on whether the considerations for RPF calculation as outlined in Sections 5.6 and 5.7 are scientifically justified and adequately described.

Chapter 6: Selection of PAHs for Inclusion in the Relative Potency Approach

This chapter describes the selection of PAHs for inclusion in the RPF approach. The evaluation focuses on whether the available data were adequate to assess the carcinogenic potential of each compound. If the data were not considered adequate, then the PAH was excluded.

6a. Please comment on whether the rationale for the weight-of-evidence evaluation is scientifically justified and adequately described. Please comment on whether the approach adequately considers the available information. Please comment on whether other information (e.g., additional structure-activity) could contribute further to the weight-of-evidence evaluation and how this information could be utilized in the analysis.

6b. The weight-of-evidence analysis does not include data related to Ah-receptor binding, cytotoxicity or tumor promotion. Please comment on whether the scientific rationale for this decision is appropriate. If these data should be considered in the derivation of RPFs, please describe how they should be incorporated into the analysis.

6c. The analysis uses an RPF detection limit as a means of comparing positive and nonpositive (or negative) bioassays. Please comment on whether this method is scientifically justified and adequately described.

6d. Graphic arrays of the calculated RPFs (Figures 6-2 through 6-35) are presented as a means of representing the variability in RPFs from different data sources, the weight-of-evidence for carcinogenic potential, and the basis for the selected RPF. Please comment on whether the figures are informative and adequately described. Please comment on whether there is other information that should be included in the figures. Please comment on whether the narratives are informative and complete.

Chapter 7: Derivation of RPFs for Selected PAHs

This chapter describes various methods (e.g. prioritization of studies) and different approaches for deriving final RPFs (e.g., arithmetic mean). Final RPFs were derived by averaging the individual study RPFs (across all exposure routes) calculated from bioassay data for PAHs that had at least one RPF based on a bioassay. The exception was dibenz[a,c]anthracene, where the RPF was calculated from cancer-related endpoint data.

7a. Please comment on the scientific justification for the approach for deriving the final RPFs and the discussion of alternative options for the estimation of the final RPFs. Please comment on the reporting of the range of RPFs as a measure of variability instead of a confidence interval. Please comment on whether the data are adequate to support more (or less) precision in deriving the RPFs.

7b. Please comment on whether the scientific rationale for consideration of bioassay data versus cancer-related endpoint data has been adequately described. Please comment on whether the cancer-related endpoint data could be used in a more quantitative manner. Please comment on the justification of the final RPF derived for dibenz[a,c]anthracene. Please comment on the use of tumor multiplicity data in the weight-of-evidence evaluations and for the determination of the RPFs.

7c. Please comment on whether the recommendation to apply the proposed RPFs across all routes of exposure is adequately described. Please comment on whether there is additional scientific information that would inform this recommendation. Please comment on whether the available data are adequate to recommend exposure route- or target organ-specific RPFs.

7d. Please comment on whether the scientific rationale for the assignment of an RPF of zero for some PAHs is adequately described. Please comment on whether there are other data that should be considered to assess whether an RPF of zero is appropriate. Please comment on whether the scientific rationale for assigning no RPF based on inadequate data for some PAHs is adequately described. Please comment on whether there are alternative methods for assigning RPFs to these PAHs. Please comment on whether the text provides adequate distinction between PAHs with RPFs of zero and PAHs with no selected RPF and whether this distinction is useful for describing uncertainty in determining the cancer risk associated with PAH exposure.

7e. The final RPFs are characterized with confidence ratings. Please comment on whether the rationale for the confidence ratings is appropriately described. Please comment on whether there are other approaches for describing confidence using the available data that could be applied in either a qualitative or quantitative manner that would be more useful for risk assessment.

Chapter 8. Uncertainties and Limitations Associated with the RPF Approach

This chapter discusses the uncertainties and limitations associated with using the RPF approach for PAH mixtures risk assessment. Many of the general uncertainties related to chemical-specific risk assessment are also applicable to the proposed RPF approach for PAHs. In addition, uncertainties exist regarding the selection of data and dose-response assessment methodology, the selection of PAHs for inclusion in the analysis, the derivation of the final RPF, the assumption of a common mode of action and dose additivity, and the extrapolation of RPFs across exposure routes.

8. Please comment on whether, overall, the document describes the uncertainties and limitations in the methodology used to derive RPFs in a transparent manner. Please comment on whether the most important uncertainties and limitations are identified. Please comment on whether there is existing information that could be used to evaluate the accuracy or validity of the RPF values to predict the cancer risk associated with exposure to PAH mixtures.

Appendices

9. Please comment on whether the information in the Appendices is adequate to allow independent verification of the calculated RPFs. If not, please comment on what additional information would be useful.