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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

DATE

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 utilizes 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, utilizing 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 asked the SAB to provide recommendations on the scientific soundness and rationale of the PAH Mixtures document in several areas: 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, which held a public meeting from June 21-23, 2010 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 Panel finds the document to be logical, clear, and concise. However, the Panel does not find the scientific basis for the RPF approach to be well justified in the document. Nevertheless, the Panel recognizes the pragmatic need for the RPF approach, and based upon the currently available data, generally agrees with EPA's use of the RPF approach for assessing PAH mixtures. The Panel agrees with EPA's decision to update the 1993 approach by increasing

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1 the number of compounds in the approach, and including the most recent data in calculating and
2 expanding the RPF values for PAHs. The Panel encourages the Agency to complete this
3 document and has recommendations to strengthen the document with regards to the selection of
4 studies, methods for dose-response modeling, and calculations of final RPFs.
5

6 The Panel agrees with EPA's selection of benzo[a]pyrene (BaP) as the index compound
7 for the RPF approach. However, the current cancer slope factor for BaP is outdated and in order
8 to estimate the risk of PAH mixtures, an up-to-date cancer slope factor for BaP is essential. The
9 Panel urges the Agency to quickly finalize the BaP assessment.
10

11 The Panel recommends that EPA pursue developing a whole mixtures approach for PAHs.
12 The Agency should set this as a strategic initiative, with a specific timeline and benchmarks, that
13 lays the foundation for an underlying concerted research program. The Panel recommends that
14 the Agency seek support from the National Toxicology Program (NTP) and/or other entities to
15 test a portfolio of 12-15 different complex PAH mixtures, using animal bioassay studies. These
16 complex PAH mixtures should represent a diverse array of mixtures, but also represent the most
17 important PAH mixture classes of concern to EPA. The Panel believes that, with these data in
18 hand, EPA could then potentially validate the RPF approach and could also potentially replace
19 the RPF approach for assessing cancer risk of PAH mixtures.
20

21 The SAB appreciates the opportunity to provide EPA with advice. We look forward to
22 receiving the Agency's response.
23

24
25 Sincerely,
26
27
28
29

30
31 Dr. Deborah L. Swackhamer
32 Chair
33 EPA Science Advisory Board

Dr. Nancy K. Kim
Chair
PAH Mixtures Review Panel

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U.S. Environmental Protection Agency
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1 **ACRONYMS**

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4 BaP Benzo[a]pyrene

5 BMD Benchmark Dose

6 BMDL Benchmark Dose (Lower Confidence Limit)

7 BMR Benchmark Response

8 CSF Cancer Slope Factor

9 EPA Environmental Protection Agency

10 IARC International Agency for Research on Cancer

11 IRIS Integrated Risk Information System

12 NCEA EPA's National Center for Environmental Assessment

13 ORD EPA's Office of Research Development

14 PAH Polycyclic Aromatic Hydrocarbon

15 RPF Relative Potency Factor

16 SAB Science Advisory Board

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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) Polycyclic Aromatic Hydrocarbon (PAH) Mixtures Review Panel review the PAH Mixtures Review 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 major recommendations from the Panel are highlighted below.

Overall Scientific Soundness of the RPF Approach

Overall, the Panel finds the document to be logical, clear, and concise. However, the Panel does not find the scientific basis for the RPF approach to be well justified in the document. Nevertheless, 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 the most recent data in calculating and expanding the RPF values for PAHs and recommends that the Agency finalize the document based upon the Panel's comments and recommendations.

The Panel recommends that EPA pursue developing a whole mixtures approach for PAHs to potentially validate the RPF approach and to serve as a possible replacement for the RPF approach in the near future. The Panel recommends that the Agency seek support from the National Toxicology Program (NTP) and/or other entities to test a portfolio of 12-15 different complex PAH mixtures of concern to EPA, using animal bioassay studies.

Rationale for Recommending an RPF Approach

EPA's document presents the scientific rationale for recommending an RPF approach for PAH mixtures. The Panel does not find the scientific basis for the proposed RPF approach to be well justified in the document. There are two basic assumptions that are proposed for applying the dose-additivity model used in the RPF approach: that the PAHs in the mixture act by a similar toxicological manner and that no significant interactions occur at low, environmentally relevant doses. The document itself cites data that call into question both of these underlying

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1 assumptions. The document discusses a number of other uncertainties that further undermine the
2 logical and scientific basis for the assumptions on which the RPF method is based.

3
4 Despite these concerns, in recognizing the pragmatic need for the RPF approach and
5 completion of the document, the Panel recommends including a discussion on EPA's previous
6 considerations about implementing a whole mixtures approach and the rationale behind the
7 decision to pursue the RPF approach.

8
9 Additionally, the Panel has the following comments and/or recommendations:

- 10
- 11 • The Panel finds that the choice of BaP as the index chemical is well justified and is
12 appropriately described for this RPF approach. The Panel urges the Agency to
13 quickly finalize the BaP assessment.
 - 14 • The Panel recommends that the assumption that PAHs, as a class, act in a similar
15 toxicological manner should be de-emphasized as a rationale for using the RPF
16 approach and that a stronger argument should be made for emphasizing comparisons
17 of actual cancer bioassay data.
 - 18 • The Panel finds that EPA's assumption that interactions among PAH mixture
19 components do not occur at low levels of environmental exposure is not scientifically
20 well justified. However, in the absence of data that support a specific interaction
21 (additive, sub- or super-additive, etc.), a default assumption of additivity is a
22 reasonable assumption for the purposes of the RPF analysis.
- 23

24 *Discussion of Previously Published RPF Values*

25

26 EPA presents a background on how RPFs have been derived in the past. The Panel
27 believes that the document adequately summarizes the previous RPF approaches, but could be
28 improved by providing more quantitative information, and editing Table 3-1 to use a
29 standardized approach for reporting values (same significant figures, scale, etc.).

30

31 *Evaluation of the Carcinogenicity of Individual PAHs*

32

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

38

39 One of EPA's study selection criteria is the stipulation that BaP must be tested
40 concurrently with the target PAH being considered. This restriction raises the concern that
41 quality animal bioassay studies may be dismissed. The Panel recommends that EPA consider
42 exploring an approach where the target PAH that was tested with BaP could serve as a surrogate
43 for BaP in studies where BaP was not tested concurrently. This may allow for additional quality
44 studies to be included. However, in considering this alternative approach, EPA should also take

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1 into account factors that could potentially outweigh the benefits in the establishment of a RPF for
2 a specific PAH, such as cross-study and cross-laboratory comparability issues.

3
4 The Panel believes that a quality assessment should be done for each individual study.
5 The Panel recommends including information such as sample size, dosing, mortality (prior to
6 tumor development), test compound purity, and whether or not the data utilized are derived from
7 tumor incidence or multiplicity.

8
9 *Methods for Dose-Response Assessment and RPF Calculation*

10
11 EPA presents the selection of dose-response data and methods for dose-response
12 assessment and RPF calculation. For quantal data (i.e. tumor incidence), EPA used the multi-
13 stage cancer model. The Panel agrees with EPA's use of the multi-stage cancer model for
14 quantal data, but has specific recommendations on the parameterization of the model. The Panel
15 also recommends that EPA provide further detail on the assumptions regarding the distribution
16 of data and further detail on the parameterization of the model.

17
18 For continuous data (i.e. tumor counts), EPA used a linear model to calculate the
19 benchmark dose (BMD). The Panel finds that the justification for using a linear model for
20 multidose continuous data is insufficient and recommends that EPA provide further justification
21 on the use of a linear model. The Panel further recommends that the modeling strategy for
22 continuous data include polynomial models or nonlinear models (e.g., the Hill model) that are
23 flexible enough to fit the data and would also adequately approximate a linear relationship.

24
25 Additionally, the Panel has the following comments and/or recommendations:

- 26
27
- 28 • The Panel agrees with EPA's derivation of RPFs from the BMDs (as opposed to the
29 lower confidence limit of the BMDs), in order to accommodate comparison of studies
30 with different precision. The Panel does not believe that any alternative approaches
31 are necessary.
 - 32 • The Panel recommends that when multiple doses are available for dose-response
33 modeling, all the data should be used with a sufficiently flexible model, e.g., the
34 multi-stage cancer model or a polynomial model for continuous endpoints.
 - 35 • The Panel is concerned about using high-BMR values to calculate RPFs and
36 recommends that the BMR be in the low-dose region.
 - 37 • The Panel recommends that when single-dose studies are used to calculate the RPF,
38 the impact on the RPF calculation should be described.

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

40
41 EPA describes the selection of PAHs for inclusion in the RPF approach. The Panel finds
42 that the method for selecting the PAHs appears to be scientifically justified, but several issues
43 such as individual study quality and study design variability across studies are incompletely
44 considered. The Panel recommends that a list of quality criteria be defined, articulated, and

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1 applied *a priori*, prior to the weight of the evidence evaluation. Only studies of sufficient quality
2 should be considered in the weight-of-evidence evaluation. The Panel recommends that once a
3 study is considered to have sufficient quality, the variability of study design characteristics
4 between studies be carefully considered prior to inclusion in the RPF calculation. Differences
5 among studies in some of these design characteristics may significantly affect the dose-response
6 within each study, which in turn, will affect the RPF calculation.

7
8 Additionally, the Panel has the following comments and/or recommendations:
9

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

23
24 *Derivation of RPFs for Selected PAHs*
25

26 EPA describes various methods (e.g. prioritization of studies) and different averaging
27 approaches for deriving final RPFs. The Panel has several reservations regarding the RPF
28 calculation approach. The Panel is concerned about calculating RPFs based upon a single
29 experiment as well as calculating RPFs using studies where there was only a single-dose level of
30 BaP and/or the target PAH, particularly if it was a high dose. The Panel does not recommend
31 calculating an RPF when only a single dose of the target PAH and only a single dose of BaP are
32 available. An RPF can be calculated from only a single dose of BaP (if the tumor incidence is in
33 the low-dose range) when adequate dose response data are available for the target PAH. The
34 Agency is encouraged to continue evaluating other methods, such as using a geometric mean
35 instead of an arithmetic mean. Using a geometric mean would give less weight to outlier values.
36

37 The Panel strongly believes that use of cancer bioassay data is essential for determining
38 the RPF for a given PAH. Cancer-related endpoint data are useful as supporting data but the
39 Panel does not recommend the use of only cancer-related endpoint data for determining the RPF.
40 Therefore, the Panel does not recommend calculating an RPF for dibenz[a,c]anthracene and
41 recommends that it be removed from Table 7.2 until further bioassay data become available.
42
43
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1 Additionally, the Panel has the following comments and/or recommendations:
2

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

19
20 *Uncertainties and Limitations Associated with the RPF Approach*
21

22 EPA discusses the uncertainties and limitations associated with using the RPF approach
23 for PAH mixtures risk assessment. The Panel finds that the uncertainties in the methodology of
24 deriving RPFs are well described. The major methodological uncertainties are clearly defined
25 and discussed such that there is little doubt about the methods that were used and the limitations
26 of the final RPF values reported. The Panel has the following recommendations to strengthen
27 this section of the document:
28

- 29 • Include comparisons of cancer risk estimates of complex mixtures using the RPF
30 approach and bioassay data.
- 31 • Include a discussion on the relevance of high doses in animal studies to the much
32 lower doses experienced by humans.
- 33 • Include a discussion on bioavailability.
- 34 • Include a discussion the uncertainty that arises from the difficulty and limitation of
35 completely characterizing mixtures.

36
37 *Adequacy of Appendices for Independent Verification*
38

39 The appendices in the document include dose-response data for potency calculations,
40 benchmark dose modeling outputs, and calculation of RPFs to allow independent verification of
41 the calculated RPFs. The Panel finds the appendices to be generally useful for verifying the
42 calculations of the RPFs, but has the following recommendations:
43

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- 1
 - 2
 - 3
 - 4
 - 5
 - 6
- 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).

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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 because they are the most widely studied members of the PAH chemical class. 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. 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.

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3. RESPONSE TO EPA CHARGE QUESTIONS

3.1. Charge Question 1 – Overall Scientific Soundness of the RPF Approach

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. However, the Panel does not believe that the scientific basis for the RPF approach is well justified. Nevertheless, 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 PAH mixtures. The Panel agrees with EPA's decision to update the 1993 approach by increasing the number of compounds in the approach, and including the most recent data in calculating and expanding the RPF values for PAHs and recommends that the Agency finalize the document based upon the Panel's comments and recommendations.

The Panel recommends that EPA begin developing a comparative/surrogate 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. The Panel believes that, with these data in hand, one could then potentially validate the RPF approach and also compare a real world 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 real world samples for which RPF compound values are known.

In parallel with the bioassay testing, the Agency should support research to develop a suite of short-term assays and biomarkers. These assays and biomarkers could be used as indicators both in animal studies and human epidemiology studies.

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

3
4 The Panel finds that the PAH Mixtures document does not provide an adequate context
5 for how the proposed RPF approach could be used in a PAH mixtures risk assessment. The
6 Panel recommends that more discussion is needed to provide this context, including moving
7 relevant portions from Chapter 7 into earlier sections of the document and providing an example.
8

9 **3.2. Charge Question 2 – Rationale for Recommending an RPF Approach**

10
11 *Chapter 2 presents the rationale for recommending an RPF approach. In an RPF approach,*
12 *doses of component chemicals that act in a toxicologically similar manner are added together,*
13 *after scaling the doses relative to the potency of an index chemical. Benzo[a]pyrene (B[a]P) is*
14 *selected as the index compound for this RPF approach. The RPF approach involves two key*
15 *assumptions related to the application of a dose-additivity model: (1) PAH components in the*
16 *mixture act in a similar toxicological manner; and (2) interactions among PAH mixture*
17 *components do not occur at low levels of exposure typically encountered in the environment.*

18
19 *2a. Please comment on whether the report provides adequate justification for using an RPF*
20 *approach as a scientifically defensible method to assess the cancer risk associated with exposure*
21 *to PAH mixtures.*

22
23 At the face-to-face meeting, the Panel discussed this issue in considerable detail, and
24 concluded that this charge question actually represents two distinct questions: first whether,
25 based on available literature, there is a sound scientific foundation for use of the single-agent
26 relative potency factor (RPF) approach, particularly with respect to the two core assumptions of
27 this rationale that were proposed in the PAH Mixtures document; and second, whether there is a
28 reasonable practical consideration in using the RPF approach at this time, independent of the
29 scientific foundation and underlying assumptions. The rationale for this dichotomy is outlined
30 below.

31
32 With regard to the first question, the Panel concludes that the scientific basis for the
33 proposed RPF approach is not well justified in the current document. There are two basic
34 assumptions that are proposed in the document as the basis for considering the RPF approach
35 specifically for PAHs: first, that the chemicals of comparison are all assumed to act by a similar
36 mechanism as the reference compound (i.e., benzo[a]pyrene - BaP), allowing one to model them
37 relative to each other based on this reference compound; and second, that their effects are
38 additive by assuming no significant interactions at low, environmentally relevant doses.
39

40 The Panel considered the PAH Mixtures document, the studies cited within, as well as
41 other data. The document discusses studies that call into question both of the underlying core
42 assumptions and further elaborates on a number of other uncertainties, some of which cannot
43 currently be validated or dismissed, that further undermine the logical and scientific basis for the

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1 assumptions on which the RPF method is based. These are discussed in more detail in response
2 to charge questions 2c and 2d below, but are briefly summarized here. It is not clear that the first
3 assumption – i.e., that the other PAHs under consideration all act by a similar mechanism as BaP
4 - is required as a foundation for the RPF method, since for these particular PAHs the method is
5 based on the outcomes of cancer bioassays, rather than the underlying mechanism(s). There are
6 also results, some of which are discussed in the document, that call into question the second
7 assumption – i.e., that there are no significant low-level interactions of PAHs in a mixture
8 beyond simple additivity, and therefore that the effects (cancer risks) of a mixture of agents are
9 the simple sum of the individual risks. This could be tested by a direct comparison of a surrogate
10 mixture of key compounds to BaP as a single agent and to a real world complex mixture such as
11 coal tar in a cancer bioassay, but results to date suggest that these PAH mixtures may, in fact,
12 produce cancer risks that are different than simple additivity might predict.
13

14 Despite these concerns about the underlying scientific justification for the RPF method
15 and the logic of the two core assumptions, the Panel concludes that there is adequate practical
16 justification for continuing to use this approach in the near term to assess cancer risk of PAH
17 mixtures in the absence of a good alternative. In particular, although this Panel and previous
18 expert panels have strongly suggested that the EPA move toward a whole mixtures-based
19 approach, the fact remains that the regulatory and scientific communities do not have sufficient
20 information to adopt a whole mixtures approach for risk assessment at this time. Therefore, the
21 Panel recommends the continued use of the component-based RPF approach as the most
22 practical choice but recommends that this should be pursued in parallel with continued
23 development of one or more whole mixtures-based approaches that could potentially validate the
24 approach and could potentially replace it.
25

26 Given these conclusions, the Panel has several recommendations for revising the
27 document and moving forward with the RPF approach. First, additional historical perspective
28 should be included in the revised document, since it is an important component in, and
29 justification for the agency's practical decision to pursue the RPF method. In particular, a
30 summary of the previous discussions about moving to a whole mixtures approach, and the
31 Agency's own evaluation of the significant data gaps that currently preclude them from doing so,
32 should be included in the second chapter. The Panel agrees with the Agency that in order to
33 continue with the RPF method, it is important to expand the number of compounds that are used
34 from the 1993 guidance, and for the most part the candidate compounds for this expanded list are
35 appropriate (see Chapter 4 discussion). The Panel also agrees that it is important to include more
36 recent data for these compounds (since 1993) in calculating and expanding the RPF values for
37 PAHs, since many of the values used in the current RPF method are based on older data. In this
38 regard the agency noted that a revised IRIS assessment of BaP is undergoing a parallel review
39 that will likely lead to a revised cancer slope factor (CSF) as well as separate values for oral,
40 dermal and inhalation BaP exposures. An up-to-date estimate of the CSF for BaP is central to
41 the validity of the RPF method since this is the index compound, and the Panel urges the Agency
42 to quickly finalize the BaP assessment.
43

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1 *2b. Please comment on whether the choice of benzo[a]pyrene as the index compound is*
2 *scientifically justified and appropriately described. Please identify and provide the rationale for*
3 *any alternative index compound(s) that should be considered.*
4

5 The choice of BaP as the index compound is well justified and is appropriately described
6 for this RPF approach. It is the best studied PAH and meets the criteria for an index compound
7 for an RPF assessment. However, it should be noted that the first core assumption of this
8 document, that the other PAHs under consideration act via a similar mechanism, by definition,
9 can lead to a choice of only those polycyclic aromatic compounds (which include substituted
10 PAHs and PAH heterocyclic derivatives) that are thought to act in this manner, and therefore
11 may exclude PAHs or polycyclic aromatic compounds (PACs) that act via other mechanisms, or
12 affect the behavior of the comparison compounds, and therefore contribute to cancer risk but are
13 not included in the RPF calculation. As discussed below, the RPF method does not require this
14 assumption, and therefore one could include any PAH for which cancer bioassay data are
15 available.
16

17 *2c. Please comment on whether the weight of evidence indicating that PAHs, as a chemical class,*
18 *have a similar mode of carcinogenic action has been adequately described and is scientifically*
19 *justified.*
20

21 There is some evidence that a subset of closely related PAHs have “similar” modes of
22 action for specific steps in inducing cancer as described in the document. This is not unexpected
23 since the compounds in question have already been defined in large part by their comparison to
24 BaP. However, although these compounds are “similar” at a certain level, available data indicate
25 that they each act via different precise mechanisms when examined at a more detailed level, and
26 therefore may weaken the support for this assumption. For example, even though many PAHs
27 are metabolized to reactive intermediates that then form DNA adducts at guanine residues, their
28 potency for conversion of DNA adducts to mutations varies among compounds. Moreover, the
29 pattern of guanine mutations within specific DNA sequences varies among these adducts. By
30 definition, these adducts are therefore acting by slightly different mechanisms at this level. Since
31 cancer risk can be related to mutation rate and to specific mutations within certain DNA
32 sequences, this will result in different risks even though these compounds share a similar mode
33 of action at a basic level.
34

35 Additionally, there are hundreds of other PAHs and PACs that may not act by these
36 mechanisms and that likely, particularly in complex mixtures, contribute in positive or negative
37 ways to the overall carcinogenicity of the mixture. These compounds should also be considered
38 in the RPF method if good animal bioassay data are available.
39

40 Also of importance, other PAHs in a mixture may alter the risk for known PAHs in that
41 mixture in more complicated ways that also involve different mechanisms. For example,
42 through mass action a complex mixture may contain total PAHs that collectively overwhelm the
43 levels of an individual PAH such as BaP, perhaps by 1000:1 or greater. These may collectively
44 interfere with the overall metabolism of BaP, or ratios of specific metabolites, or the capacity to

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1 repair DNA adducts from BaP, etc., such that one cannot predict the cancer risk from BaP solely
2 from its concentration in the mixture. Therefore, this assumption is not scientifically well
3 justified.
4

5 In addition, there is a question as to whether similar modes of action are sufficient to
6 predict *in vivo* carcinogenicity. As discussed in the PAH Mixtures document (e.g., page 35,
7 section 2.6), mutagenicity, genotoxicity and similar short-term assays are relatively poor
8 predictors of *in vivo* carcinogenesis. Yet a basic assumption of the document is that this
9 mechanistic information is sufficient to predict their relative carcinogenicity. There are PAHs
10 that are positive in short-term *in vitro* assays but negative or weak in animal bioassays, and vice
11 versa, further undercutting this basic assumption.
12

13 The document also discusses the role of the Ah receptor (AhR) in detail as another
14 potential unifying mechanism for carcinogenic PAHs, but elsewhere also acknowledges that
15 interaction with and activation of the AhR is not a good indicator of promotion or *in vivo*
16 tumorigenesis for PAHs (as opposed to dioxins). The Panel agrees with this latter assessment,
17 and therefore recommends removing this discussion and consideration of this mechanism.
18

19 Taken together, these points argue that this basic assumption of the RPF model is not
20 well justified based on available data. More importantly, the RPF method may not require this
21 assumption since it is based on the ultimate endpoint, cancer. In fact, the RPF method is
22 completely independent of, and does not require any mechanistic understanding so long as there
23 are good animal bioassay data that can generate a slope for an RPF comparison to BaP. Thus,
24 the mechanistic underpinnings should be de-emphasized as a rationale for RPF and a stronger
25 argument should be made for emphasizing actual cancer bioassay data to directly compare PAHs
26 alone and in mixtures. Mechanistic information on BaP could be referenced from other
27 comprehensive sources such as IRIS and International Agency for Research on Cancer (IARC)
28 monographs, or other recent literature reviews. Because of the lack of predictive power for data
29 from short-term assays and the lack of correlation between these mechanistically-based assays
30 and tumor outcome, these should not be used in the RPF approach.
31

32 *2d. Please comment on whether the assumption that interactions among PAH mixture*
33 *components do not occur at low levels of exposure typically encountered in the environment has*
34 *been adequately described and is scientifically justified.*
35

36 The assumption that there are not significant interactions among PAHs in complex
37 mixtures at low doses is not scientifically well justified. As discussed in the document (page 23,
38 lines 11-19) coal tar behaved very differently in *in vivo* carcinogenesis assays than would be
39 predicted from studies with BaP as a single agent, or what would likely be predicted from a RPF
40 approach based on BaP as a single agent. Likewise, as discussed in the document (page 39, lines
41 3-12 and Table 2-2), the complex and unpredictable results to date of simple binary
42 combinations of PAHs that do not follow simple additivity also undercuts both scientific
43 assumptions of the RPF approach. However, in the absence of consistent data that support a
44 specific type of interaction (additive, sub- or super-additive, etc.) that could be used for a variety

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1 of PAH mixtures, a default assumption of additivity is a reasonable assumption for the purposes
2 of the RPF analysis.

3
4 It should be noted, however, that complex mixtures such as coal tar, MGP residues,
5 creosote, diesel exhaust and other PAH mixtures contain hundreds of other compounds, not
6 included in this RPF assessment, that likely contribute to the overall biological effects of the
7 mixtures. Other contributing mechanisms may include: induction or suppression of specific
8 metabolic pathways; competition for metabolism through mass action at active sites; epigenetic
9 effects; promotion and progression effects; endocrine disruption, neurological and
10 immunological effects that contribute to cancer risk; and other classes of potentially potent
11 carcinogens including substituted PAHs, volatile organic compounds (VOCs), metals, and other
12 compounds. Collectively, these mechanisms may contribute in complicated ways to the overall
13 cancer risk of a complex mixture, further reinforcing the recommendation to explore moving in a
14 concerted way from a component-based RPF approach to a whole mixtures-based approach,
15 which would remove some of these uncertainties.

16
17 **3.3. Charge Question 3 – Discussion of Previously Published RPF Approaches**

18
19 *This chapter presents a discussion of previously published RPF approaches. Due to the*
20 *evolution of the state of the science and an increased understanding of PAH toxicology, EPA is*
21 *reevaluating the RPF approach for PAHs in this analysis.*

22
23 *3. Please comment on whether the discussion provides a meaningful background on how RPFs*
24 *have been derived in the past, and the advantages and disadvantages of previous methods.*

25
26 This chapter adequately summarizes the previous RPF approaches, but could be
27 improved by providing more quantitative information, and editing Table 3-1 to use a
28 standardized approach for reporting values (same significant figures, scale, etc.).

29
30 **3.4. Charge Question 4 – Evaluation of the Carcinogenicity of Individual PAHs**

31
32 *This chapter discusses the development of a database of primary literature on PAH*
33 *carcinogenicity and cancer-related endpoints and the criteria used to include or exclude studies*
34 *from the database.*

35
36 *4a. Please comment on whether the list of 74 PAHs (Table 2-1) included in the initial literature*
37 *search is complete. Please comment on whether the rationale for the choice of PAHs included in*
38 *the literature search has been appropriately described. Please identify other databases or*
39 *resources that should be included.*

40
41 Chapter 4 of the PAH Mixtures document details the basis for the selection criteria that
42 was used to develop the database related to PAH carcinogenicity and cancer-related endpoints.

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1 The list of 74 PAHs provided in Table 2-1 is believed by the Panel to be reasonable in view of
2 the criteria of having three or more fused rings and not containing heteroatoms, alkyl or nitro
3 substituents. The development of the database of primary literature on PAH carcinogenicity and
4 cancer-related endpoints and the criteria used to include or exclude studies from the database are
5 described in detail within this chapter. The database appears adequate, with the recommendation
6 that a recently published IARC Monograph on PAHs, Volume 92, be included as an additional
7 resource (IARC, 2010).

8
9 *4b. Chapter 4 includes a description of how studies were selected for use in dose-response*
10 *assessment. Please comment on whether the choices and assumptions in making the selection*
11 *have been adequately described. Please comment on whether the information in Tables 4-1*
12 *through 4-14 provides adequate information to inform how decisions were made. Please*
13 *comment on whether studies were rejected or included appropriately. Please comment on*
14 *whether positive and nonpositive studies have been considered appropriately.*

15
16 The basis for selecting which studies were used in dose-response assessment is clearly
17 delineated. The information in Tables 4-1 through 4-14 provides adequate information related to
18 whether certain studies were rejected or included in this document. However, the criteria for
19 including or rejecting a study should be revised to include only studies that are deemed to be of
20 sufficient quality using *a priori* standards as described in the response to charge question 6a.
21 Given this revision of including only high quality studies, the EPA approach inappropriately
22 discards data that do not achieve statistical significance. Please see the response to charge
23 question 6a for further detail.

24
25 *4c. The methodology for the choice of studies to use in the derivation of RPFs includes studies*
26 *where at least one PAH was tested at the same time as B[a]P. Studies where individual PAHs*
27 *were tested without concurrent testing of B[a]P were not included in the quantification of RPFs.*
28 *Please comment on the scientific rationale for this approach. Please comment on whether the*
29 *advantages and disadvantages of excluding certain data from the derivation of RPFs have been*
30 *adequately described.*

31
32 Chapter 4 of the document stipulates that BaP had to be tested concurrently for inclusion
33 of a study on the carcinogenicity or other cancer-related endpoints of one or more of these 74
34 PAHs. This restriction raises a concern that quality carcinogenicity studies might be dismissed.
35 The Panel recommends that EPA consider whether a PAH other than BaP, with a RPF that has a
36 comparatively narrow range, might be able to serve as the surrogate for the BaP index compound
37 in those instances where BaP was not included in a bioassay. This approach offers the
38 possibility that additional quality studies could be to be included in the development of a RPF for
39 a given PAH. The Panel recommends that this be examined especially in those instances where
40 limited animal bioassay data were used to establish a RPF value. However, in considering this
41 alternative approach, EPA should also take into account factors that could potentially outweigh
42 the benefits in the establishment of a RPF for a specific PAH, such as cross-study and cross-
43 laboratory comparability issues.

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1 The Panel has a few recommendations that relate to the evaluation of the carcinogenicity
2 studies for individual PAHs. These recommendations include providing some quality
3 assessment to individual studies, such as a tabulation of various studies with included
4 information on: 1) sample size, 2) dosing, 3) mortality (prior to tumor development), 4) defined
5 test compound purity and 5) whether or not the data utilized are derived from tumor incidence or
6 multiplicity.

7
8 In addition, the Panel recommends incorporating or reiterating some of the discussion
9 about alternatives for ranking RPFs provided in Appendix G into the discussions on individual
10 PAHs in Chapter 4 as well as in Chapter 6. For example, the Panel considers the discussion
11 about the influence of the route of administration on the RPF calculations to be particularly
12 informative.

13
14 **3.5. Charge Question 5 – Methods for Dose-Response Assessment and RPF Calculation**

15
16 *This chapter describes the selection of dose-response data and methods for dose-response*
17 *assessment and RPF calculation from the selected datasets. The methodology for estimation of*
18 *the RPFs varied depending on the characteristics of the datasets, however, the general equation*
19 *was the ratio of the slope of the dose-response curve for the subject PAH to the slope of the dose-*
20 *response curve for B[a]P.*

21
22 *5a. Please comment on whether the scientific rationale for the dose-response modeling*
23 *approaches used in the derivation of RPFs is adequately described. Please comment on whether*
24 *there are other appropriate modeling approaches for estimating the relative potencies of PAHs.*
25 *Please describe alternative approaches (e.g., other model forms) that could be considered.*

26
27 The modeling approaches described in Chapter 5 of this document for multi-dose studies
28 are based on whether the data are quantal (binary) or continuous. The quantal endpoints
29 considered in this document include tumor incidence or incidence of cancer-related endpoints,
30 including frequency of mutations per number of cells interrogated. The continuous endpoints
31 include tumor counts (number of tumors per animal) or cancer-related endpoints of a continuous-
32 variable nature (e.g., number of sister chromatid exchanges, number of morphologically
33 transformed colonies).

34
35 When modeling quantal data, the mean model is for the probability of response (e.g.,
36 tumor incidence) and is generally assumed to follow a sigmoid-shape. Commonly used models
37 that could be used include the logistic, probit, multi-stage, and Gompertz models. Since the
38 multi-stage cancer model has a biological basis, it is the standard model used for cancer
39 incidence and is considered sufficiently flexible to accommodate the dose-response data for these
40 PAHs. Specifically, the multi-stage cancer model for the probability of a tumor is parameterized
41 based on the number of dose groups (g) with the polynomial assumed to equal g-2:

42
43
$$\mu = \beta_0 + (1 - \beta_0) \left[1 - \exp(\beta_1 x + \beta_2 x^2 + \dots + \beta_{g-2} x^{g-2}) \right].$$

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1 It should be noted that a model for data with g dose groups will exactly track the sample
2 means (here, sample proportions) if the degree of the polynomial is $g-1$. However, a variation of
3 this general model, typically used in risk assessment, assumes a monotonic relationship and
4 constrains all parameters to be non-negative. The Benchmark Dose (BMD) Software used in the
5 document makes such an assumption as the default analysis. With quantal data, assumed to be
6 independent across and within-dose groups, it is generally assumed that the data are binomially
7 distributed with binomial variance (i.e., with n subjects evaluated at a dose group, the variance in
8 the number “responding” is assumed to be $n\mu(1-\mu)$). Alternatively, the data may follow hyper-
9 or hypo-binomial variability, i.e., greater than or less than binomial variability. These
10 assumptions are not specified in the document and should be. The BMD Software used to
11 estimate unknown model parameters uses a maximum likelihood estimation criterion and
12 standard iterative algorithms for estimation. However, these distributional assumptions and the
13 parameterization of the multi-stage cancer model should be clearly stated in the document. It is
14 not clear whether the assumption of binomial variability was verified; the assumption of
15 binomial variability should be verified and the document should include information about the
16 verification. Instead, the model checking was based on the goodness-of-fit of the mean model
17 and did not assess the assumptions regarding variability.
18

19 For continuous endpoints, a nonlinear dose-response shape may be expected from the
20 data. However, the analysis plan for continuous endpoints is to use a linear model (i.e., a linear
21 function). The justification for using the linear model for the multi-dose continuous data is
22 insufficient and additional justification should be added. Although the linear model is the
23 simplest model, there are other models such as the Hill model or polynomial model that are
24 commonly used. EPA’s justification for using the linear model is that there are a small number
25 of dose groups. This is an inadequate explanation.
26

27 The modeling strategy for the continuous endpoints should include polynomial models or
28 nonlinear models (e.g., the Hill model) that are flexible enough to fit the data and would also
29 adequately approximate a linear relationship. In some cases, the variance in response is assumed
30 to be constant over the dose range of observed data. A least-squares (or nonlinear least squares)
31 criterion is used to estimate unknown model parameters. In contrast, the sample variance may
32 change with the mean. For example, the responses in the low-dose region may have lower
33 variance than that observed as the dose (and response) increase. Such data may be estimated
34 using a quasi-likelihood estimation criterion.
35

36 For the continuous data included in this document, the assumption about whether the
37 variance changes across the dose groups is not addressed and the potential for a nonlinear shape
38 is not allowed. Only a linear model was used to estimate the mean response. A goodness-of-fit
39 criterion was used; if the model did not provide adequate fit, high-dose groups were sequentially
40 eliminated in an effort to achieve adequate fit. This strategy is arbitrary and should be avoided.
41 A more flexible model should be used instead that accommodates the nonlinearity of the data.
42
43
44

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1 *Selection of Benchmark Response (BMR)*

2
3 Since the RPFs are going to be used to estimate cancer risks at generally low
4 environmental exposures, the calculation of RPFs should be applicable to the low-dose range,
5 preferably excess risks ≤ 0.10 for quantal data. Similarly for continuous data, the calculation of
6 RPFs should preferably be based on changes in the mean of less than or equal to one standard
7 deviation (and certainly less than two standard deviations) in order to remain in the low-dose
8 region of interest. For normally-distributed data, a change in the mean from the control mean of
9 two standard deviations will result in approximately 50% of the subjects in the abnormal range.
10 The RPF can increase or decrease substantially as dose (incidence or response) changes.

11
12 The analysis strategy described in Chapter 5 (with the suggested changes included)
13 should be specifically followed. Deviations from the planned analysis strategy should be clearly
14 explained.

15
16 To illustrate the use of a nonlinear model, the *in vitro* clastogenicity dose-response data
17 of Tong et al (1981) (Table C-19, page C-85 of PAH Mixtures document) is reanalyzed. For
18 convenience, the data table is reproduced in Table 1. The data clearly follow a nonlinear
19 relationship, which is particularly evident, considering the two highest concentrations of
20 benz[a]anthracene (BaA) that have similar responses with a log change in concentration.
21

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		7×10^{-6}
Control	0	15.75	5.18	20.9	
BaA	10^{-5}	21.2	9.59		
BaA	10^{-4}	29.15	9.93		

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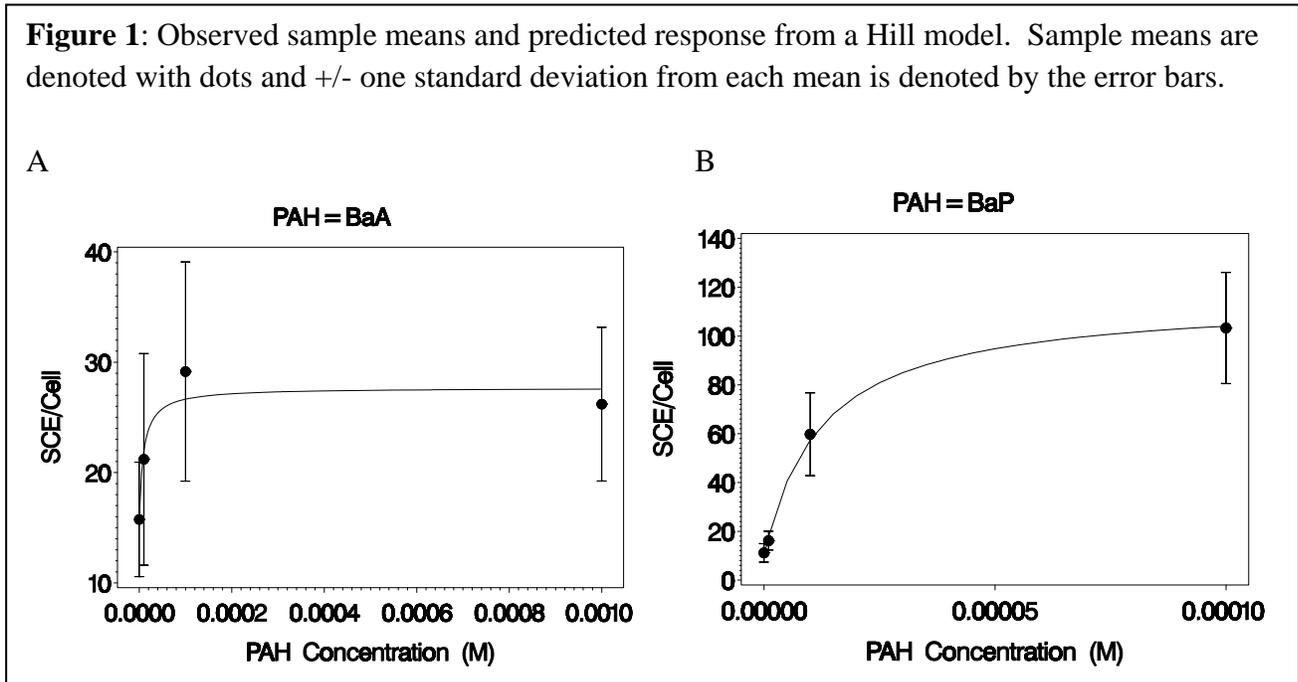
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1 Instead of fitting a linear model to these data, a 3-parameter Hill model is selected, which
2 can accommodate an asymptotic response for large concentrations, i.e.,
3

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

4
5
6 where x is the concentration of the PAH, α is the response for the control group, γ is the range of
7 response such that $\alpha + \gamma$ is the asymptote for large x . Since only sample means and standard
8 deviations are available at each concentration level, a weighted analysis is imposed, with weights
9 set to the inverse of the sample standard deviation at each concentration. Unknown parameters
10 are estimated using a weighted least squares criterion in a Gauss-Newton iterative algorithm
11 using PROC NLIN in SAS (version 9.2). The resulting predicted models for BaP and BaA are
12 provided in Figure 1. Using all of the data, a Hill model adequately fits the observed sample
13 means for both PAHs.
14

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.



15
16
17 The specified BMR for continuous data is one standard deviation (SD) above the control
18 mean as predicted from the Hill model (shown in Table 1). For BaP, the estimated BMD_{1SD} is
19 4×10^{-7} and for BaA, the estimate is 7×10^{-6} . However, in Table E-14 (page E-31), the BMR and
20 BMD values are blank and the point estimate responses are 92 and 13 for BaP and BaA,
21 respectively; and the point estimate dose is 1×10^{-4} for both compounds. It is not clear how the
22 point estimate responses were calculated. This is an example where the described analysis plan
23 does not seem to be followed without any explanation of why it was not followed.
24
25

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1 *5b. For each individual dataset considered in the assessment, the B[a]P dose-response was*
2 *calculated from the study-specific data. Please comment on whether this approach has been*
3 *appropriately described. If there are additional approaches using the available data that should*
4 *be considered, please describe how the approach could lead to a better estimate of cancer risk.*
5

6 The strategy of using study-specific data for the BaP dose-response with PAH dose-
7 response is advantageous since downstream calculations are intra-study and avoid comparisons
8 without accounting for study effects. This strategy has been appropriately described and the
9 Panel does not have other approaches to suggest.

10
11 It should be noted that the estimates of BaP slope across studies with different
12 characteristics are very different. The range of the estimates can be more than 1,000 fold. This
13 supports the idea of using study-specific estimates for calculating the RPFs.
14

15 *5c. The point of departure for slope estimation that has been used for the derivation of RPFs is*
16 *the benchmark dose (BMD) estimate rather than the lower confidence limit on the benchmark*
17 *dose (BMDL). Please comment on whether this approach is scientifically justified and*
18 *adequately described. Please comment on whether alternative approaches should be considered.*
19

20 It is correct to base the derivation of the RPFs on the estimate derived from the BMD,
21 rather than the lower confidence limit on the benchmark dose (BMDL), in order to obtain an
22 estimate of the total exposure for a mixture (expressed as the total BaP equivalent dose). Due to
23 chance experimental variation, some of the RPFs will be overestimated and some will be
24 underestimated. These biases will tend to cancel each other for the total exposure of a mixture.
25 On the other hand, when the study sizes are similar, the BMDLs between the BaP and PAH may
26 be stable. But when the two studies have different precision, the ratio of BMDLs is tenuous.
27 Therefore, the ratio of BMDs is advisable. The Panel does not believe that any alternative
28 approaches are necessary.
29

30 *5d. Please comment on the methodology used for the RPF calculations for multidose and single*
31 *dose datasets. Please comment on whether the process for calculating RPFs from the various*
32 *datasets is scientifically justified and adequately described. Please comment on the utilization of*
33 *high response levels in some instances as the point of comparison. Please describe alternative*
34 *approaches that could lead to a better estimate of cancer risk that should be considered using*
35 *the available data. Please comment on whether the considerations for RPF calculation as*
36 *outlined in Sections 5.6 and 5.7 are scientifically justified and adequately*
37 *described.*
38

39 When multiple doses are available for dose-response modeling, all of the data should be
40 used with a sufficiently flexible model, e.g., the multi-stage cancer model or a polynomial model
41 for continuous endpoints. An example of such an analysis strategy is given in 5a above. In the
42 Appendix, there are cases where single-dose data were used when multiple doses were available;
43 this should be explained.
44

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1 Generally, the Panel is concerned about using high-BMR values to calculate the RPFs in
2 single-dose studies. If the dose-response curves were parallel across PAHs, then the choice of
3 BMR would not impact the estimation of a relative potency factor. However, as discussed in
4 earlier chapters, it is generally assumed that the chemicals are not dilutions of one another, so
5 their dose-response curves will generally not be parallel. Thus, the choice of the BMR should be
6 in the low dose-region. However, in some special cases, the RPF calculation is not dependent on
7 the response level. For example, consider the data from a BaP single-dose study and multi-dose
8 comparison PAH for benzo[k]fluoranthene (BkF) (LaVoie et al, 1982). For convenience, the
9 data from Table C-1, page C-4 of the PAH Mixtures document are reproduced below in Table 2.
10
11

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

12
13
14
15 Suppose a one-stage model is used for analysis of the single-point BaP study, i.e.,
16

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

17
18 where $\beta_0 = 0$, x is the dose of BaP, and β_1 is the unknown parameter associated with the slope.
19 Assuming a zero background response rate (i.e., $\beta_0 = 0$), the BMD(10) is estimated as
20 $BMD(10) = -\log(0.9)/\beta_1$ and the BMD(85) is estimated as $BMD(85) = -\log(0.15)/\beta_1$. Since
21 there are four dose groups for BkF, a multi-stage model is used, parameterized with linear and
22 quadratic terms (i.e., $g-2 = 2$ for a second-degree model):
23
24

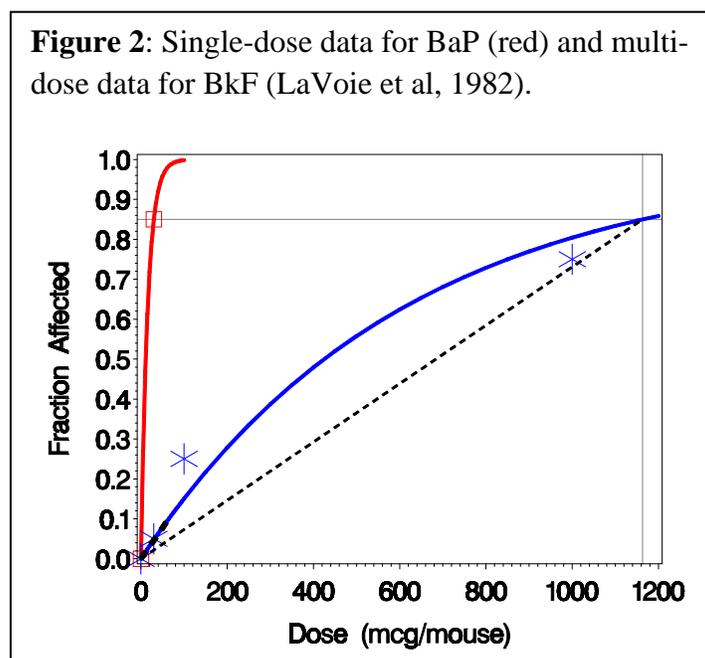
$$\mu = \beta_0 + (1 - \beta_0)[1 - \exp(-\beta_1 x - \beta_2 x^2)]$$

25
26

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1 where x is the dose of BkF and again we assume $\beta_0=0$. However, in the EPA document, β_2 was
 2 set to zero and the one-stage model was used due to convergence problems. Therefore the same
 3 parameterization is used for both BaP and BkF. The fitted dose-response curves are provided in
 4 Figure 2. Notice the predicted response from the single-dose study is the sample mean (here,
 5 observed sample proportion).
 6



7
 8
 9 When the one-stage model is used for both chemicals, the choice of BMR is not relevant
 10 in the calculation of the RPF. Consider the following algebraic manipulations to demonstrate for
 11 a general $BMR=\mu_0$ and for a general j^{th} PAH:
 12

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

14
 15 Thus, the RPF is not a function of the BMR when a one-stage model is used for both the BaP and
 16 comparison PAH. To illustrate from the LaVoie (1982) data, the results for a BMR of 10% and
 17 85% (the observed response from BaP) are given in Table 3. The resulting RPFs are identical.

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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.

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1 The Panel believes that the method for selecting the PAH appears to be scientifically
2 justified, but has recommendations about several issues that are incompletely considered. These
3 issues include: (1) the quality of the individual studies considered and (2) the variability of other
4 design characteristics among studies, and how this may weigh on their evaluation prior to
5 inclusion in the weight-of-evidence evaluation or calculation of an RPF.
6

7 Regarding the quality of individual studies being considered, the Panel recommends that a
8 list of quality criteria should be defined, articulated, and applied *a priori* (e.g., methodologically
9 robust, such as inclusion of an adequate control group, sample size, dose level, number of doses,
10 number of PAHs measured, purity of the compounds considered, etc.) prior to the weight-of-
11 evidence evaluation. This information should be illustrated in the form of tables or individual
12 graphs. Only studies of sufficient quality, as defined *a priori*, should be considered in the
13 weight-of-evidence evaluation.
14

15 The Panel recommends that once a study is considered to have sufficient quality, the
16 variability of other study characteristics among studies should be carefully considered prior to
17 their use in the calculation of the RPF. Some of these study characteristics include: species,
18 strain and sex of animal model, route of exposure, form of exposure (injection, implantation,
19 etc.), frequency of administration, exposure duration, location of tumors, types of tumors
20 (papillomas, adenomas, carcinomas etc.), and stage of tumors (benign, malignant). Differences
21 among studies in some of these characteristics may significantly affect the dose-response within
22 each study, which in turn, will affect the RPF calculation. For example, for a given PAH one
23 may have one study that used skin tumorigenesis and another that used implantation of solid
24 material intratracheally. The latter study, if positive, might add weight to the overall
25 determination that the PAH is tumorigenic in animals, but may be a poor study from which to
26 calculate dose-response or relative potency. Or one could be comparing one study that has a
27 physiological exposure route such as inhalation, ingestion, or dermal application, with one with a
28 non-physiological exposure such as an intraperitoneal or implantation study. Likewise, there are
29 tumor models, such as the A/J mouse, where tumor multiplicity counting is required due to the
30 high penetrance of tumor response. It is not a simple task to reconcile these studies with other
31 studies of tumor incidence for the purposes of quantitatively assessing dose-response.
32

33 There is no simple formulaic method for determining, *a priori*, how to include or exclude
34 such studies or how to weight them, since this will vary depending on the individual PAH and
35 also depending on what studies are available; it also requires a measure of expert scientific
36 judgment. Instead, the Agency should clearly articulate the quality criteria (e.g., expand and
37 articulate the characteristics listed in Table 7.1), and then only use studies with adequate quality
38 to calculate RPFs. Weighting factors may be required for inclusion of some studies for RPF
39 calculations, or they may only be valuable as a qualitative, weight-of-evidence assessment of
40 carcinogenicity rather than for quantitative RPF calculations. The criteria for how such decisions
41 are made for each study and each PAH should be clearly defined and described by the Agency as
42 part of its assessment.
43

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1 The EPA approach inappropriately discards data that do not achieve statistical
2 significance. Lack of statistical significance does not necessarily mean that an effect is zero. It
3 could be that there is an effect with biological relevance, but the sample sizes were too small to
4 achieve statistical significance. Using a cutoff P-value of 0.05 for inclusion of data in the
5 weight-of-evidence assessment is arbitrary. It can create a scenario where there are two studies
6 of equally high quality and one study is included because it has a P-value = 0.04 and the other
7 study is not included because it has a P-value = 0.06. A quality study that produces a low
8 statistically non-significant RPF is relevant and must be included in calculating the best
9 (weighted average) estimate for an RPF. Discarding values in the lower tail of a statistical
10 distribution, solely due to lack of statistical significance, results in a biased estimate of the effect.

11
12 *6b. The weight-of-evidence analysis does not include data related to Ah-receptor binding,*
13 *cytotoxicity or tumor promotion. Please comment on whether the scientific rationale for this*
14 *decision is appropriate. If these data should be considered in the derivation of RPFs, please*
15 *describe how they should be incorporated into the analysis.*

16
17 The Panel finds that the rationale for omission of Ah-receptor data is well justified.
18 Additional information is not necessary. The Panel also agrees with EPA's decision that once
19 information demonstrating tumor formation is obtained, additional information on cytotoxicity
20 and tumor promotion is not necessary. However, the document should clearly state the reasons
21 for the omission of these data.

22
23 *6c. The analysis uses an RPF detection limit as a means of comparing positive and nonpositive*
24 *(or negative) bioassays. Please comment on whether this method is scientifically justified and*
25 *adequately described.*

26
27 EPA employed the use of an "RPF detection limit" to evaluate the results of positive and
28 nonpositive results in the same test system. The "RPF detection limit" was defined as the RPF
29 determined by the lowest response that would have been statistically significant for the subject
30 PAH and the actual benzo[a]pyrene response. The Panel did not find this definition to be clear
31 nor did the Panel find the description of the use of "RPF detection limits" to be clear. The Panel
32 does not recommend utilizing statistical significance as a means to determine which studies to
33 include or exclude. As discussed above, the Panel recommends assessing study quality to
34 determine which studies to include or exclude from the weight-of-evidence evaluation. It is
35 scientifically incorrect to discard data of sufficient high quality that do not achieve statistical
36 significance and therefore, the Panel does not recommend using "RPF detection limits" for that
37 purpose.

38
39 *6d. Graphic arrays of the calculated RPFs (Figures 6-2 through 6-35) are presented as a means*
40 *of representing the variability in RPFs from different data sources, the weight-of-evidence for*
41 *carcinogenic potential, and the basis for the selected RPF. Please comment on whether the*
42 *figures are informative and adequately described. Please comment on whether there is other*
43 *information that should be included in the figures. Please comment on whether the narratives*
44 *are informative and complete.*

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1 The Panel finds that Figures 6-2 through 6-35 provide a good summary of the individual
2 studies considered and the variability of individual RPF estimates across studies. However, the
3 Panel recommends clearly indicating which studies were used to estimate the final RPF. This
4 would make the figures much more informative.
5

6 With respect to the presentation of RPFs for individual studies, the Panel proposes that
7 rather than graphically displaying the RPF for each individual study as a bar, it can be shown as
8 a point estimate coupled with information on variability (e.g., standard error, standard deviation,
9 confidence interval, and range). The information on variability in the study is viewed as key, to
10 help the reader interpret the study findings.
11

12 The Panel recommends that, for ease of reading and to ensure completeness, the
13 narratives be presented in a consistent structure and format, both in terms of the information
14 presented, as well as the order in which they are presented. The Panel also recommends
15 integrating information provided in Appendix G into the narratives that correspond to Figures 6-
16 2 through 6-35.
17

18 **3.7. Charge Question 7 – Derivation of RPFs for Selected PAHs**

19
20 *This chapter describes various methods (e.g. prioritization of studies) and different approaches*
21 *for deriving final RPFs (e.g., arithmetic mean). Final RPFs were derived by averaging the*
22 *individual study RPFs (across all exposure routes) calculated from bioassay data for PAHs that*
23 *had at least one RPF based on a bioassay. The exception was dibenz[a,c]anthracene, where the*
24 *RPF was calculated from cancer-related endpoint data.*
25

26 *7a. Please comment on the scientific justification for the approach for deriving the final RPFs*
27 *and the discussion of alternative options for the estimation of the final RPFs. Please comment*
28 *on the reporting of the range of RPFs as a measure of variability instead of a confidence interval.*
29 *Please comment on whether the data are adequate to support more (or less) precision in*
30 *deriving the RPFs.*
31

32 The Panel believes that presenting the range instead of a confidence interval is
33 appropriate. The Panel does have reservations regarding several aspects of the RPF calculation
34 approach. First, the Panel has concerns regarding calculating RPFs based upon a single
35 experiment (e.g., 11H-benz[b,c]aceanthrylene, benzo[g,h,i]perylene, benzo[e]aceanthrylene,
36 benz[j]aceanthrylene, dibenzo[a,h]pyrene, indeno[1,2,3-c,d]pyrene and naphtho[2,3-e]pyrene).
37 Second, there is concern regarding the use of data for calculating RPF values in which there was
38 only a single-dose level of BaP and/or the other PAH being evaluated (e.g., benz[a]anthracene,
39 11H-benz[b,c]aceanthrylene, benzo[e]aceanthrylene, naphtho[2,3-e]pyrene and fluoranthene),
40 particularly if it was a high dose. The Panel does not recommend calculating an RPF when only
41 a single dose of a PAH and only a single dose of BaP are available. An RPF can be calculated
42 from only a single dose of BaP when dose response data are available for the PAH. Since the
43 RPF varies with the level of the tumor incidence, RPFs should only be calculated from a single

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1 dose of BaP if the tumor incidence at the dose of BaP is in the low-dose range; certainly, only if
2 the BaP tumor incidence is less than 50%. Finally, there is concern about calculating the
3 arithmetic mean for PAHs that have markedly divergent individual RPFs (e.g., benzo[c]fluorene).
4 The Agency is encouraged to continue evaluating other methods, such as using a geometric mean
5 instead of an arithmetic mean. Where sufficient data are available, the use of a geometric mean
6 would give less weight to outlier values. Further, examination of the variability for estimates of
7 RPFs in several of the figures indicates that a log-normal distribution may be appropriate to
8 describe the variability of RPFs. Hence, the geometric mean would be a better estimate of
9 central tendency. Also, the best central estimate would be a weighted geometric mean where the
10 weights are inversely proportional to the square of the standard errors. That is, RPFs with large
11 standard errors would receive less weight. The Panel believes that calculating RPFs to one
12 significant figure is appropriate.

13
14 *7b. Please comment on whether the scientific rationale for consideration of bioassay data*
15 *versus cancer-related endpoint data has been adequately described. Please comment on*
16 *whether the cancer-related endpoint data could be used in a more quantitative manner. Please*
17 *comment on the justification of the final RPF derived for dibenz[a,c]anthracene. Please*
18 *comment on the use of tumor multiplicity data in the weight-of-evidence evaluations and for the*
19 *determination of the RPFs.*

20
21 The Panel believes that the scientific rationale for considering bioassay data versus
22 cancer-related endpoint data has been adequately described. The Panel strongly believes that the
23 use of cancer bioassay data is essential for determining the RPF for a given PAH. Cancer-related
24 endpoint data are useful as supporting data, but the Panel does not recommend the use of only
25 cancer-related endpoint data for determining the RPF. As such, the Panel does not have
26 recommendations on how to use cancer-related endpoint data in a more quantitative manner.
27 The Panel does not recommend calculating an RPF for dibenz[a,c]anthracene and recommends
28 that it be removed from Table 7.2 until further bioassay data become available.

29
30 The Panel recommends that additional information and justification be provided for the
31 inclusion or exclusion of cancer bioassay data for PAHs that did not give significant tumor
32 responses in well-designed studies. One suggestion is to include the IARC classification for
33 those PAHs where a classification exists in Table 7.1 or perhaps in Table 7.3. The Panel
34 believes that there is a need for some additional measure of the quality of individual studies used
35 in determining the final RPF values. This is important in addition to the confidence ratings
36 provided in Table 7.3 (see also further discussion below). The Panel also strongly believes that
37 more cancer bioassay data with mixtures would be extremely helpful in further validating the
38 RPF approach.

39
40 Tumor multiplicity (continuous data; average number of tumors per mouse) and tumor
41 incidence (quantal data; percentage of mice with tumors) represent different measures of
42 tumorigenicity/carcinogenicity. In the document, RPFs calculated from tumor multiplicity data
43 are combined with other RPFs calculated from tumor incidence data to calculate final RPFs. An
44 example of the problem is benzo[c]fluorene. The divergent RPFs used to calculate the final RPF

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1 value for benzo[c]fluorene in Table 7.1 come from averaging a study where multiplicity data
2 were used (RPF of 50) and one where incidence data were used (RPF of 1). It is recommended
3 that RPF values not be averaged from these two different measures without sufficient
4 justification for using the multiplicity data. In this regard, accurate assessment of differences in
5 potency using tumor multiplicity requires adequate dose-response data. For accurate
6 comparisons, at least 3 doses of each PAH should be available for comparison. In addition, these
7 doses should be distributed across the dose-response range and not be clustered on the high or
8 low end of the dose response range. In lieu of adequate dose-response data for tumor
9 multiplicity, the Panel recommends that only tumor incidence data be used to calculate final
10 RPFs. Additionally, if calculated RPFs for a given PAH still remain divergent across multiple
11 well-designed studies due to multiple factors (e.g., combining incidence and multiplicity,
12 combining data from different organs, combining data from different routes of exposure, etc) the
13 Agency may wish to consider use of the geometric mean in place of the arithmetic mean as
14 discussed above.

15

16 *7c. Please comment on whether the recommendation to apply the proposed RPFs across all*
17 *routes of exposure is adequately described. Please comment on whether there is additional*
18 *scientific information that would inform this recommendation. Please comment on whether the*
19 *available data are adequate to recommend exposure route-or target organ-specific RPFs.*

20

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

42

43

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1 *7d. Please comment on whether the scientific rationale for the assignment of an RPF of zero for*
2 *some PAHs is adequately described. Please comment on whether there are other data that*
3 *should be considered to assess whether an RPF of zero is appropriate. Please comment on*
4 *whether the scientific rationale for assigning no RPF based on inadequate data for some PAHs*
5 *is adequately described. Please comment on whether there are alternative methods for assigning*
6 *RPFs to these PAHs. Please comment on whether the text provides adequate distinction between*
7 *PAHs with RPFs of zero and PAHs with no selected RPF and whether this distinction is useful*
8 *for describing uncertainty in determining the cancer risk associated with PAH exposure.*
9

10 The Panel generally believes that the scientific rationale presented in the document for
11 assignment of an RPF of zero, the assignment of no RPF, and the distinction between them is
12 adequately described. However, the Panel does have concern regarding the quality of the data
13 used to assign an RPF of zero for some studies and also regarding the inconsistent use of studies
14 with RPFs of zero in calculating the final RPFs. The Panel recommends that a consistent
15 approach be adopted for using RPFs of zero for all compounds for which final RPFs are
16 calculated. In addition, the Panel recommends that the Agency continue to evaluate how RPFs
17 of zero are calculated as well as the rationale for assigning no selected RPF values. In addition,
18 the Panel recommends the Agency discontinue assigning a value of zero to quality studies that
19 have non-statistically significant results. See the response to charge question 6a for further
20 details.

21
22 *7e. The final RPFs are characterized with confidence ratings. Please comment on whether the*
23 *rationale for the confidence ratings is appropriately described. Please comment on whether*
24 *there are other approaches for describing confidence using the available data that could be*
25 *applied in either a qualitative or quantitative manner that would be more useful for risk*
26 *assessment.*
27

28 In general, the Panel believes that characterizing the final RPFs with confidence ratings is
29 a good idea. However, the confidence ratings do not appear to give any indication of the overall
30 quality of the data being assessed and used for the RPF calculation. Based on the information
31 provided in Table 7.3, confidence ratings appear to be related to the number of studies used, data
32 from more than one route of exposure, presence of non-cancer endpoint supporting data to
33 calculate the RPFs, etc. The Panel strongly believes that there needs to be some measure of the
34 quality of the individual studies used to generate the RPFs. In this context, quality refers to
35 study characteristics, such as sample size and statistical power, presence or absence of non-lethal
36 toxicity, unusual mortality, and other potential confounding factors. Also, the Panel makes
37 several recommendations for calculating RPFs; depending on EPA's final RPF approach, these
38 recommendations may be useful in developing confidence ratings.
39

40 Chapter 7 also includes a description of how the RPF method is used to calculate relative
41 cancer risk from exposure to PAH mixtures (section 7.3). In addition, there is a section (section
42 7.4) dealing with the use of age-dependent adjustment factors (ADAFs) to adjust for differences
43 in susceptibility during early life (i.e., <16 years of age). The Panel believes that these two
44 sections are extremely important to the overall presentation of the document and are somehow

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1 lost by inclusion at the end of Chapter 7. It is strongly recommended that the information on
2 cancer risk assessment (sections 7.3 and 7.4) be moved to the beginning of the document as a
3 separate section.
4

5 **3.8. Charge Question 8 – Uncertainties and Limitations Associated with the RPF**
6 **Approach**

7
8 *This chapter discusses the uncertainties and limitations associated with using the RPF approach*
9 *for PAH mixtures risk assessment. Many of the general uncertainties related to chemical-*
10 *specific risk assessment are also applicable to the proposed RPF approach for PAHs. In*
11 *addition, uncertainties exist regarding the selection of data and dose-response assessment*
12 *methodology, the selection of PAHs for inclusion in the analysis, the derivation of the final RPF,*
13 *the assumption of a common mode of action and dose additivity, and the extrapolation of RPFs*
14 *across exposure routes.*

15
16 *8. Please comment on whether, overall, the document describes the uncertainties and limitations*
17 *in the methodology used to derive RPFs in a transparent manner. Please comment on whether*
18 *the most important uncertainties and limitations are identified. Please comment on whether*
19 *there is existing information that could be used to evaluate the accuracy or validity of the RPF*
20 *values to predict the cancer risk associated with exposure to PAH mixtures.*

21
22 The uncertainties in the methodology of deriving RPFs are described quite well in the
23 PAH Mixtures document. The major methodological uncertainties are clearly defined and
24 discussed so that there is little doubt about the methods that were used and the limitations of the
25 final RPF values reported.

26
27 In evaluating the average RPF values, the quality of the source material should be
28 evaluated rather than giving equal weight to each in calculating average RPF values. Some type
29 of weighting scheme needs to be developed for RPFs based on the quantity and quality of
30 existing data. For studies of suitable quality, the best statistical estimate for the RPF is a
31 weighted mean of the individual RPFs, where the weight assigned an individual RPF is the
32 reciprocal of the square of its standard error. Larger sample sizes produce smaller standard
33 errors resulting in more weight.

34
35 Existence of a common mode of action is not necessary in order to apply the RPF
36 approach. The discussion of the mode of action in the document should be reduced considerably
37 by utilizing brief references to relevant literature that discusses the current knowledge of the
38 three mechanisms of metabolic activation of PAHs. There is growing evidence that PAHs and
39 other related compounds in complex mixtures, such as coal tar / MGP residue, can act by other
40 non-genotoxic and mutagenic mechanisms. Such mechanisms include acting as endocrine
41 disruptors, epigenetic agents, by causing immunologic and neurologic effects, and other non-
42 genotoxic effects that may contribute to cancer risk. Genotoxicity and mutagenicity are but one
43 of many ways that environmental agents can contribute to cancer risk. PAHs in mixtures can

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1 also affect each others' metabolism and toxicokinetics in complex and poorly predicted ways -
2 for example, by induction or suppression of specific metabolic enzymes and pathways, by
3 competition for active site metabolism of key enzymes, by altering cell proliferation and
4 differentiation, and other factors that affect metabolism, distribution, toxicokinetics, potency, and
5 the dose-response curve. Although the individual doses of specific PAHs in a complex mixture
6 may be small, their cumulative amount may be sufficient to interact in these non-additive
7 manners that are not described by the simple mechanisms assumed for BaP and similar PAHs
8 described in the document.

9
10 More data dealing with the comparisons of the RPF approach and estimates of cancer risk
11 derived from complex mixtures are needed, which would reduce some of the uncertainties
12 associated with the RPF approach described in the document. The feasibility of directly studying
13 complex mixtures is illustrated by the limited pair of existing data sets. Chronic bioassays in
14 mice for two synthesized coal tar mixtures were conducted at the National Center for
15 Toxicological Research, Food and Drug Administration (Culp et al., 1998). The RPF approach
16 applied to these data were reported in the Electric Power Research Institute (EPRI) public
17 comments (Rohr, 2010). Comparisons of cancer risk observed in the chronic animal bioassays
18 for the two coal tar mixtures were within a factor of two to four (lower) of the cancer risks based
19 on the RPF approach. This is an encouraging result for use of the RPF approach, albeit for only
20 two mixtures. Additional comparisons, such as those submitted by EPRI, should be added to the
21 document as it provides very useful information about the RPF approach. Statistical variation of
22 cancer risk estimates between chronic animal bioassays on the order of three to four is expected
23 (Gaylor et al., 2000). More data dealing with the comparisons of the RPF approach and
24 estimates of cancer from tested mixtures are needed.

25
26 Additional mixtures of PAHs need to be studied in chronic animal bioassays in order to
27 compare the observed cancer risk of a mixture with the risk estimated from the RPF approach.
28 Section 3.1 of the PAH Mixtures document discusses the availability of several studies on
29 mixtures that provide data for comparing cancer risk estimates using the RPF approach with
30 direct estimates of risk from the mixtures. Unfortunately, no quantitative information was
31 presented in the document to indicate the potential size of uncertainty for the RPF approach.
32 This quantitative information needs to be added to the document in order to evaluate the
33 accuracy and precision of the RPF approach from existing examples.

34
35 The cancer slope factor for BaP is multiplied by the RPFs in order to obtain cancer unit
36 risk factors for each of the PAHs. Hence, the cancer unit risk factor for BaP is critical to the
37 calculation of the cancer risk estimate for a mixture using the RPF approach. Based on old
38 studies, the upper limit of the cancer unit risk factor for lifetime oral exposure to BaP is
39 7.3×10^{-3} per $\mu\text{g}/\text{kg}$ per day listed in the EPA Integrated Risk Information System (IRIS), 1994.
40 Based on a Good Laboratory Practice (GLP) study the upper limit of the cancer unit risk factor
41 for BaP is 1.2×10^{-3} per $\mu\text{g}/\text{kg}$ per day (Gaylor et al., 2000). Because of the relatively large
42 uncertainty in the cancer unit risk factor for BaP, this value needs to be updated before reliable
43 estimates of cancer risk can be derived for mixtures of PAHs.

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1 Extending the classes of PAH should be considered by incorporating other PAH
2 derivatives, e.g., PACs that occur in mixtures, particularly where bioassays exist such as for
3 nitro-aromatics and alkylated PAHs.
4

5 The relevance of high doses in animal studies to the much lower doses experienced by
6 humans is not discussed in the document. The Panel recommends that this additional
7 information be added.
8

9 The state of a single PAH administered to animals in bioassays may be different from the
10 state of the same PAHs in mixtures where they may not be easily desorbed from solid particles.
11 The bioavailability to humans for PAHs in a mixture needs to be compared to the bioavailability
12 in animal bioassay experiments that utilize purified PAH compounds. Cancer risk estimates
13 based on the RPF values and the total concentration of PAH in mixtures may be overestimated.
14

15 Using measured concentrations of PAHs in mixtures, sensitivity analyses can indicate
16 which uncertainties in individual RPFs have a significant impact on the total BaP equivalents for
17 a mixture. EPA should consider adding this to the document, perhaps by using the mixtures
18 discussed in the EPRI comments.
19

20 More PAHs could be included, where concurrent data on BaP were not collected, by
21 calculating the RPF of the PAH to a second PAH and calculating the RPF of this second PAH to
22 BaP. Then, the RPF of the PAH to BaP is the product of these two intermediate RPFs. Although
23 less direct and potentially less accurate than the concurrent bioassays that include the BaP
24 reference-based RPF method, this approach could prove useful for identifying additional PAH
25 candidates for inclusion in a secondary RPF data set. The Panel recommends that this be
26 examined especially in those instances where limited animal bioassay data were used to establish
27 a RPF value. However, in considering this alternative approach, EPA should also take into
28 account factors that could potentially outweigh the benefits in the establishment of a RPF for a
29 specific PAH, such as cross-study and cross-laboratory comparability issues.
30

31 The composition for each individual mixture must be adequately determined, otherwise
32 uncertainty is added to the RPF approach. Completely characterizing mixtures is difficult, and
33 this limitation and uncertainty should be discussed. For example, different PAHs may have
34 different effects on the induction phase I and/or phase II enzymes that might affect the metabolic
35 activation or deactivation of other potentially highly tumorigenic PAHs, i.e., a non-additive
36 effect as mentioned in the PAH Mixtures document. Various PAHs may inhibit each other.
37 Mixtures may or may not contain substances that act as promoters of tumorigenesis rather than
38 as genotoxic initiators. Without adequately characterizing mixtures, these effects may not be
39 considered.
40
41
42

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1 **3.9. Charge Question 9 – Adequacy of Appendices for Independent Verification**

2
3 *9. Please comment on whether the information in the Appendices is adequate to allow*
4 *independent verification of the calculated RPFs. If not, please comment on what additional*
5 *information would be useful.*
6

7 There are 7 appendices in the document and the information contained in them include: a
8 bibliography of secondary sources reviewed for identification of primary literature, a
9 bibliography of studies without BaP as a reference compound, dose-response data for potency
10 calculations, benchmark dose modeling outputs, calculation of RPFs, an example calculation of
11 an RPF detection limit, and evaluation of alternatives for ranking RPFs.
12

13 The appendices are generally useful for verifying the calculations of the RPFs. However,
14 the Panel recommends reorganizing the appendices by chemical (with each identified in the
15 Table of Contents). This would include the corresponding BaP data for each study within each
16 chemical section which may be repeated across PAHs.
17

18 The plots from the Benchmark Dose Software output are useful but it should be noted
19 that the linear extrapolation to the origin is based on BMDLs instead of BMDs. The calculation
20 of the multi-stage cancer slope factor is also given based on the BMDL instead of the BMD. The
21 Panel recommends that the slope factors be added to these appendices based on the BMD –
22 which is the approach taken in the document.
23

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1 **4. REFERENCES**

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APPENDIX – CHARGE QUESTIONS

NCEA 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.

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1 **General Charge Questions**

2
3 1a. Please comment on whether the report is logical, clear and concise. Please comment on
4 whether EPA has clearly synthesized the scientific evidence for the derivation of relative
5 potency factors for individual PAHs.

6
7 1b. Please comment on whether the report provides adequate context for how the proposed RPF
8 approach could be used in a PAH mixtures risk assessment.

9
10 **Chapter 2. Rationale for Recommending an RPF Approach**

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

18
19 2a. Please comment on whether the report provides adequate justification for using an RPF
20 approach as a scientifically defensible method to assess the cancer risk associated with
21 exposure to PAH mixtures.

22
23 2b Please comment on whether the choice of benzo[a]pyrene as the index compound is
24 scientifically justified and appropriately described. Please identify and provide the rationale
25 for any alternative index compound(s) that should be considered.

26
27 2c. Please comment on whether the weight of evidence indicating that PAHs, as a chemical class,
28 have a similar mode of carcinogenic action has been adequately described and is
29 scientifically justified.

30
31 2d. Please comment on whether the assumption that interactions among PAH mixture
32 components do not occur at low levels of exposure typically encountered in the environment
33 has been adequately described and is scientifically justified.

34
35 **Chapter 3. Discussion of Previously Published RPF Approaches**

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

39
40 3. Please comment on whether the discussion provides a meaningful background on how RPFs
41 have been derived in the past, and the advantages and disadvantages of previous methods.

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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.

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- 1 5c. The point of departure for slope estimation that has been used for the derivation of RPFs is
2 the benchmark dose (BMD) estimate rather than the lower confidence limit on the
3 benchmark dose (BMDL). Please comment on whether this approach is scientifically
4 justified and adequately described. Please comment on whether alternative approaches
5 should be considered.
6
- 7 5d. Please comment on the methodology used for the RPF calculations for multidose and single
8 dose datasets. Please comment on whether the process for calculating RPFs from the various
9 datasets is scientifically justified and adequately described. Please comment on the
10 utilization of high response levels in some instances as the point of comparison. Please
11 describe alternative approaches that could lead to a better estimate of cancer risk that should
12 be considered using the available data. Please comment on whether the considerations for
13 RPF calculation as outlined in Sections 5.6 and 5.7 are scientifically justified and adequately
14 described.
15

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

17 This chapter describes the selection of PAHs for inclusion in the RPF approach. The evaluation
18 focuses on whether the available data were adequate to assess the carcinogenic potential of each
19 compound. If the data were not considered adequate, then the PAH was excluded.
20

- 21 6a. Please comment on whether the rationale for the weight-of-evidence evaluation is
22 scientifically justified and adequately described. Please comment on whether the approach
23 adequately considers the available information. Please comment on whether other
24 information (e.g., additional structure-activity) could contribute further to the weight-of-
25 evidence evaluation and how this information could be utilized in the analysis.
26
- 27 6b. The weight-of-evidence analysis does not include data related to Ah-receptor binding,
28 cytotoxicity or tumor promotion. Please comment on whether the scientific rationale for this
29 decision is appropriate. If these data should be considered in the derivation of RPFs, please
30 describe how they should be incorporated into the analysis.
31
- 32 6c. The analysis uses an RPF detection limit as a means of comparing positive and nonpositive
33 (or negative) bioassays. Please comment on whether this method is scientifically justified
34 and adequately described.
35
- 36 6d. Graphic arrays of the calculated RPFs (Figures 6-2 through 6-35) are presented as a means of
37 representing the variability in RPFs from different data sources, the weight-of-evidence for
38 carcinogenic potential, and the basis for the selected RPF. Please comment on whether the
39 figures are informative and adequately described. Please comment on whether there is other
40 information that should be included in the figures. Please comment on whether the narratives
41 are informative and complete.
42
43
44

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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.

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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.