Draft Charge to External Reviewers for the Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures for the IRIS Program
September 2009

The U.S. Environmental Protection Agency (EPA) 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 prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

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

Chapter 1. Background, Scope of Work, and Relationship to the Development of a PAH Mixtures Health Assessment

1. Does the report provide adequate context for the use of an RPF approach within a PAH mixtures assessment?

Chapter 2. Rationale for Recommending an RPF Approach

2. Does the report provide adequate justification for including an RPF approach as a scientifically defensible method to assess the cancer risk associated with exposure to PAH mixtures?

3. Is the list of 74 PAHs included in the initial literature search complete? Was the literature search sufficiently broad and inclusive? Has the scientific rationale for the choice of PAHs included in the literature search been appropriately described? Are there other databases or resources that should be included?

4. Benzo[a]pyrene (B[a]P) is utilized as the index compound for the RPF approach. Has this scientific justification for this choice been appropriately described? Please identify and provide the rationale for alternative index compound(s) that should be considered.

5. Does the text adequately describe and evaluate the current weight of evidence supporting the assumption that PAHs as a chemical class have a similar mode of action? Does the document adequately discuss the degree to which this hypothesis and other data support the assumption of additivity that is a key component of a RPF approach?

Chapter 3. Discussion of Previously Published RPF Approaches

6. Is the discussion of previously published RPF approaches complete? Does it provide a meaningful background on how RPFs have been derived in the past, and the advantages and disadvantages of previous methods?

Chapter 4. Evaluation of the Carcinogenicity of Individual PAHs

7. Is the database of primary literature relevant to the RPF approach transparently and objectively described? Are the criteria used to select studies for inclusion in the assessment adequately described? Are there additional criteria that should be considered?

8. The methodology for the derivation of RPFs includes only studies where at least one PAH was tested at the same time as B[a]P. There are other studies available where a PAH was tested without concurrent testing of B[a]P, but where comparable B[a]P data are available from the same laboratory and test system. Should these data be used to estimate RPFs? Please discuss any advantages or disadvantages of excluding these data.

9. Tables of study summary information are used to show how studies were selected for use in dose-response assessment. Have the choices and assumptions in making the selection been adequately described? Do the tables provide adequate information to inform how the decisions were made? Were studies rejected or included appropriately?

10. Do the sections describing different study types (e.g., 4.3.1-4.3.3) adequately explain the variety of methods used?

Chapter 5: Methods for Dose Response Assessment and RPF Calculation

11. Is the scientific rationale for the dose-response modeling approaches used in the derivation of RPFs adequaely described? Please describe alternative approaches (e.g., other model forms) that should be considered.

12. For each individual dataset considered in the assessment, the slope of the B[a]P dose-response was calculated from the study-specific data. An alternative approach would be to pool the B[a]P data from different studies in the same test system and use a single B[a]P slope to calculate all RPFs for that test system. Please comment on whether this alternative approach or additional approaches should be considered.

13. The point of departure for slope estimation that has been used is the benchmark dose estimate (BMD) rather than the lower confidence limit on the benchmark dose (BMDL) as this estimate is considered to be a more stable basis for comparison between the potencies of benzo[a]pyrene and the selected PAH. Has the rationale been adequately described? Please comment on whether alternative approaches should be considered.

14. Is the process for calculating RPFs from the various datasets (e.g. multidose, single dose) adequately described? Are the special considerations for RPF calculation (e.g. tumor bioassay data, cancer-related endpoint data) adequately described? Please describe alternative approaches that should be considered.

15. For bioassay data, mortalities that occurred prior to the appearance of the first tumor have not been taken into consideration, and an assumption has been made that the number of animals

at risk for tumor development is equal to the total number of animals alive at the appearance of the first tumor. Has this rationale been adequately described? Please describe alternative approaches that should be considered.

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

16. A streamlined weight-of-evidence evaluation, in the form of a decision tree, is employed to assess whether a given PAH should be included or excluded from the RPF approach. Has the scientific rationale for the decision tree been adequatley described? Does the approach adequately consider the available information? Please describe any data that conflicts with the conclusions of the decision tree for any given PAH.

17. Several studies have suggested that PAHs containing a bay or fjord region are more likely to be mutagenic and/or carcinogenic. Please comment on how this or other structure-activity information should contribute to the weight of evidence evaluation.

18. The weight of evidence analysis does not include data related to Ah-receptor binding, cytoxicity or tumor promotion. Should quantitative data for these endpoints be used in the derivation of RPFs? If so, please describe how these data should be incorporated into the assessment (e.g., how would you modify the ranking framework to accommodate the data).

19. The assessment uses a "RPF detection limit" concept as a means of comparing positive and nonpositive (negative results) bioassays. Please comment on whether the scientific justification for this concept has been adequately described. Does the approach used to estimate the "RPF detection limit" provide a meaningful metric for this comparison?

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

Chapter 7: Derivation of Summary RPFs for selected PAHs

21. Summary RPFs were derived by averaging the RPFs calculated from bioassay data for any PAH that had at least one RPF based on a bioassay. Please comment on the transparency and justification for this approach, and the discussion of alternative options for the estimation of the summary RPF. 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 precision in deriving the RPFs.

22. Please comment on whether the scientific rationale for the assignment of an RPF of zero for some PAHs is transparently and objectively described. Please comment on 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 in the decision tree based on inadequate

data for some PAHs is adequately described. Please comment on whether there are alternative methods for assigning RPFs to these PAHs.

23. Please comment on whether the approach 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.

24. Please comment on whether the scientific rationale for consideration of bioassay data versus cancer-endpoint data has been adequately described. Please comment on the use of tumor multiplicity data in the weight of evidence evaluations and for determination of the RPFs.

25. Please comment on whether the available data are adequate to recommend exposure route- or target organ-specific RPFs.

26. The selected RPFs are characterized with confidence ratings. Please comment on whether the scientific rationale for the confidence ratings is appropriately described. Please describe alternative approaches to the confidence ratings that should be considered.

Chapter 8. Uncertainties Associated with RPF Approach

27. Overall, does the report describe the scientific rationale for the methodology used to derive RPFs in a manner that is transparent and objective? Are the most important uncertainties identified?

Appendices

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