NCEA Proposed 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
February 2010

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

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

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

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

General Charge Questions

1. 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.

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

Chapter 2. Rationale for Recommending an RPF Approach

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

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

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

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

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

Chapter 3. Discussion of Previously Published RPF Approaches

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

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

Chapter 4. Evaluation of the Carcinogenicity of Individual PAHs

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

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

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

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

Chapter 5: Methods for Dose Response Assessment and RPF Calculation

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

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

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

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

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

RPF calculation as outlined in Sections 5.6 and 5.7 are scientifically justified and adequately described.

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

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

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

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

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

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

Chapter 7: Derivation of RPFs for Selected PAHs

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

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

7b. Please comment on whether the scientific rationale for consideration of bioassay data versus cancer-related endpoint data has been adequately described. Please comment on whether the cancer-related endpoint data could be used in a more quantitative manner. Please comment

on the justification of the final RPF derived for dibenz[a,c]anthracene. Please comment on the use of tumor multiplicity data in the weight-of-evidence evaluations and for the determination of the RPFs.

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

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

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

Chapter 8. Uncertainties and Limitations Associated with the RPF Approach

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

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

Appendices

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