Draft Charge to External Reviewers for the IRIS Toxicological Review of Benzo[a]pyrene
June 2011

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of benzo[a]pyrene 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). An existing IRIS assessment for benzo[a]pyrene, which includes an oral reference dose (RfD) and carcinogenicity assessment, was posted on IRIS in 1987.

The current draft health assessment includes an RfD, RfC, and carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of benzo[a]pyrene. Please provide detailed explanations for responses to the charge questions. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly presented and synthesized the scientific evidence for noncancer and cancer hazard?

2. Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review.

Chemical-Specific Charge Questions:

(A) Oral Reference Dose (RfD) for Benzo[a]pyrene

1. A 60 day toxicity study of benzo[a]pyrene in female Sprague-Dawley rats (Xu et al., 2010) was selected as the basis for the derivation of the RfD. Please comment on whether the selection of this study as the principal study is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Decreased ovary weight in female rats was selected as the critical effect for the derivation of the RfD. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. Several additional studies are available which report low dose effects following oral benzo[a]pyrene exposure (see Table 5-1). Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

3. Benchmark dose (BMD) modeling was applied to the decrease in ovary weight in female Sprague-Dawley rats to derive the point of departure (POD) for the RfD. Has the BMD

modeling been appropriately conducted and clearly described? Is the benchmark response (BMR) selected for use in deriving the POD (i.e. a 1 SD change in ovary weight) scientifically supported and clearly described? Please comment on whether this approach is scientifically supported and clearly described.

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD. Are the UFs scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

(B) Inhalation Reference Concentration (RfC) for benzo[a]pyrene

1. A developmental toxicity study (exposure on GD 11-20) of benzo[a]pyrene in F344 rats (Archibong et al., 2002) was selected as the basis for the derivation of the RfC. Please comment on whether the selection of this study as the principal study is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Decreased fetal survival and decreased pup weight in rats was selected as the critical effect for the derivation of the RfC. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

3. The NOAEL/LOAEL approach was used to derive the POD for the RfC. Please comment on whether this approach is scientifically supported and clearly described.

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. Are the UFs scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

(C) Carcinogenicity of Benzo[a]pyrene

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, benzo[a]pyrene is determined to be carcinogenic to humans by all routes of exposure. Is the cancer weight of evidence characterization scientifically supported and clearly described?

2. A mutagenic mode of action is proposed as the primary mode of action of benzo[a]pyrene carcinogenicity. Please comment on whether this determination is scientifically supported and clearly described. Please comment on data available for benzo[a]pyrene that may support an alternative primary mode of action.

Oral Slope Factor (OSF)

3. A lifetime dietary study of benzo[a]pyrene in female mice (Beland and Culp, 1998) was selected for the derivation of an OSF. Please comment on whether the selection of this study for quantitation is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected for quantitation.

4. The incidence of tumors of the alimentary tract (forestomach, esophagus, tongue, and larynx) in female mice was selected to serve as the basis for the quantitative oral cancer assessment. Please comment on whether this selection is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the OSF.

5. The OSF was calculated by linear extrapolation from the POD (i.e. the lower 95% confidence limit on the dose associated with 10% extra risk of alimentary tract tumors). Has the modeling been appropriately conducted and clearly described?

Inhalation Unit Risk (IUR)

6. A lifetime inhalation study of benzo[a]pyrene in Syrian hamsters (Thyssen et al., 1981) was selected for the derivation of an IUR. Please comment on whether the selection of this study for quantitation is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected for quantitation.

7. The incidence of upper respiratory and upper digestive tract tumors (primarily larynx and pharynx tumors) in male hamsters was selected to serve as the basis for the quantitative inhalation cancer assessment. Please comment on whether this selection is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the IUR.

8. The IUR was calculated by linear extrapolation from the POD (i.e. the lower 95% confidence limit on the concentration associated with 10% extra risk of laryngeal and pharyngeal tumors). Has the modeling been appropriately conducted and clearly described?

Dermal Slope Factor (DSF)

9. A 104-week study of benzo[a]pyrene in C3H/HeJ mice (Sivak et al., 1997) was selected for the derivation of a DSF. Please comment on whether the selection of this study for quantitation is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected for quantitation.

10. The incidence of skin tumors in male mice was selected to serve as the basis for the quantitative dermal cancer assessment. Please comment on whether this selection is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the DSF.

11. The DSF was calculated by linear extrapolation from the POD (i.e. the lower 95% confidence limit on the concentration associated with 10% extra risk of skin tumors). Has the modeling been appropriately conducted and clearly described?

12. The DSF was adjusted to account for interspecies scaling between mice and humans. This cross-species adjustment was based on allometric scaling using body weight to the 3/4 power. Under this approach, rodents and humans exposed to the same daily dose of a carcinogen, adjusted for $BW^{3/4}$, would be expected to have equal lifetime risks of cancer. However, because there is no established methodology for cross-species extrapolation of dermal toxicity, several alternative approaches were evaluated (see Appendix H). Please comment on whether the selected interspecies scaling approach is scientifically supported and clearly described. Also, please comment on whether the alternative approaches presented are scientifically supported and clearly described. Please identify and provide the rationale for any alternative approach that should be selected.