EPA Proposed Draft Charge to the Science Advisory Board for the IRIS Toxicological Review of Benzo[a]pyrene

June 2012

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the draft Toxicological Review 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 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 evaluation of human cancer potential and an oral slope factor, was posted on the IRIS database in 1987.

IRIS is a human health assessment program that evaluates qualitative and quantitative health 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.

The external review draft Toxicological Review of Benzo[a]pyrene is based on a comprehensive review of the available scientific literature on the human and animal health effects of benzo[a]pyrene, and was developed according to guidelines and technical reports published by EPA (see Preamble). This draft IRIS assessment provides an overview of the data regarding the toxicokinetics of benzo[a]pyrene in humans and animals and characterizes the potential hazard posed by benzo[a]pyrene exposure for noncancer and cancer health effects. The draft assessment also includes a qualitative characterization of the human cancer potential. In addition, a chronic oral reference dose (RfD), inhalation reference concentration (RfC), oral and dermal slope factor, and inhalation unit risk are derived.

Charge Questions

In April 2011, the National Research Council (NRC) released its "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde." In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC included comments and recommendations to improve IRIS documents generally. The IRIS Program's implementation of the NRC recommendations is following a phased approach. Phase 1 of implementation has focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments that had been near the end of the development process and close to final posting. The IRIS Program is now in Phase 2 of implementation, which addresses all of the short-term NRC recommendations. The Program is implementing all of these recommendations but recognizes that achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and external peer review committees. This phased approach is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at

the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others."

Below is a set of charge questions that address scientific issues in the draft IRIS Toxicological Review of Benzo[a]pyrene. The charge questions also seek feedback on whether the document is clear and concise, a central concern expressed in the NRC report. Please provide detailed explanations for responses to the charge questions. EPA will also consider the Science Advisory Board review panel's comments on other major scientific issues specific to the hazard identification and dose-response assessment of benzo[a]pyrene. 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 health effects of benzo[a]pyrene?

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of benzo[a]pyrene.

Chemical-Specific Charge Questions:

(A) Hazard Identification

Synthesis of Evidence

1. A synthesis of the evidence for benzo[a]pyrene toxicity is provided in Section 1, Hazard Identification. Please comment on whether the available data have been clearly and appropriately synthesized for each toxicological effect. Please comment on whether the weight of evidence for hazard identification has been clearly described and scientifically justified.

Summary and Evaluation

1. Does EPA's hazard assessment of non-cancer human health effects of benzo[a]pyrene clearly and objectively represent and synthesize the available scientific evidence to support its conclusions that benzo[a]pyrene poses a potential human health hazard for non-cancer toxicity to the immune system; the male and female reproductive systems; the developing fetus; and the nervous system in the developing fetus?

2. Does EPA's hazard assessment of the carcinogenicity of benzo[a]pyrene clearly and objectively represent and synthesize the available scientific evidence to support its conclusions that 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?

    a. 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.

(B) Dose Response Analysis

Oral reference dose (RfD) for benzo[a]pyrene

1. EPA's dose-response analysis includes the development of candidate oral reference doses (RfD) for non-cancer effects. Please comment on whether the evaluation and selection of studies and effects for the derivation of candidate RfDs is scientifically supported and clearly described. Specifically, please comment on the selection of the following studies and effects for dose-response analysis:
    a. Developmental toxicity-Chen et al. (2012) [neurodevelopmental impairment]; Jules et al. (2012) [cardiovascular effects];
    b. Reproductive toxicity-Xu et al. (2010) [decreased ovarian weights];Mohamed et al. (2010) [decreased sperm count]; and Gao et al. (2011) [increased cervical hyperplasia]
    c. Immunotoxicity-Kroese et al. (2001) [decreased thymus weights]; DeJong et al. (1999) [decreased IgM and IgA levels and number of B cells]

    Please identify and provide the rationale for any other studies or effects that should be considered.

2. Benchmark dose (BMD) modeling was applied to derive points of departure (POD) for the candidate RfDs when possible. Has the BMD modeling been appropriately conducted and clearly described? Are the benchmark responses (BMR) selected for use in deriving the PODs scientifically supported and clearly described? When BMD modeling was not possible a NOAEL/LOAEL approach was used to calculate RfDs. Please comment on whether these approaches are scientifically supported and clearly described.

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

4. Organ/system-specific RfDs were calculated based on developmental, reproductive and immune system toxicity data. These reference values may be useful for cumulative risk assessments that consider the combined effect of multiple agents acting on the same biological system. Please comment on whether the selection of these RfDs is scientifically supported and clearly described.

5. The proposed overall RfD chosen was based on neurodevelopmental impairment observed by Chen et al. (2012). Please comment on whether the selection of this RfD is scientifically supported and clearly described.

Inhalation reference concentration (RfC) for benzo[a]pyrene

1. EPA's dose-response analysis includes the development of candidate oral reference concentrations (RfC) for non-cancer effects. Please comment on whether the evaluation and selection of studies and effects for the derivation of candidate RfCs is scientifically

supported and clearly described. Specifically, please comment on the selection of the following studies and effects for dose-response analysis:

a. Developmental toxicity-Archibong et al. (2002) [decreased fetal survival]; Wormley et al., (2004) [Decreased long term potentiation in hippocampus]
b. Reproductive toxicity-Archibong et al. (2008) [decreased testes weight and sperm count and motility]

Please identify and provide the rationale for any other studies or effects that should be considered.

2. Benchmark dose (BMD) modeling was attempted to derive points of departure (PODs) for the candidate RfCs but was not feasible. The NOAEL/LOAEL approach was used to derive the PODs for the candidate RfCs. Please comment on whether this approach is scientifically supported and clearly described.

3. 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.

4. Organ/system-specific RfCs were calculated based on developmental and reproductive toxicity data. These reference values may be useful for cumulative risk assessments that consider the combined effect of multiple agents acting on the same biological system. Please comment on whether the selection of these RfCs is scientifically supported and clearly described.

5. The proposed overall RfC chosen was based on decreased fetal survival observed by Archibong et al., (2002). Please comment on whether the selection of this RfD is scientifically supported and clearly described.

Cancer risk estimates for benzo[a]pyrene

Oral Slope Factor (OSF)

1. A lifetime dietary study of benzo[a]pyrene in female mice (Beland and Culp, 1998) was selected for the derivation of the 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.

2. 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.

3. 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)

1. A lifetime inhalation study of benzo[a]pyrene in Syrian hamsters (Thyssen et al., 1981) was

selected for the derivation of the 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.

2. 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.

3. 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)

1. A lifetime study of benzo[a]pyrene in male C57L mice (Poel, 1959) and a 104-week study of benzo[a]pyrene in C3H/HeJ mice (Sivak et al., 1997) were selected for the derivation of a DSF based on increased incidence of skin tumors. 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.

2. 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?

3. 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 clearly described and whether any of these approaches should be selected as the recommended approach. Please identify and provide the rationale for any alternative approach that should be selected.