Charge to External Reviewers for the IRIS Toxicological Review of Biphenyl

September 2011

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the draft Toxicological Review of Biphenyl 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). The existing IRIS assessment for biphenyl includes a chronic reference dose (RfD) posted in 1989 and a cancer weight-of-evidence descriptor posted in 1991. The external review draft Toxicological Review of Biphenyl includes an RfD and a cancer assessment.

Charge Questions

Below is a set of charge questions that address scientific issues in the draft Toxicological Review of Biphenyl. Please provide detailed explanations for responses to the charge questions. EPA will also consider reviewer comments on other major scientific issues specific to the hazard identification and dose-response assessment of biphenyl. Please identify and provide the rationale for approaches to resolve the issues where possible. 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 biphenyl?

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 biphenyl.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for biphenyl

1. A developmental toxicity study of biphenyl in Wistar rats (Khera et al., 1979) was selected as the basis for the derivation of the RfD. Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the RfD, please identify this study and provide scientific support for this choice.

2. A developmental effect in Wistar rats (i.e., fetal skeletal anomalies) was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfD. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different endpoint is recommended as the critical effect for deriving the RfD, please identify this effect and provide scientific support for this choice.

3. Benchmark dose (BMD) modeling was conducted using the incidence of litters with fetal skeletal anomalies to estimate the point of departure (POD) for derivation of the RfD. Has the modeling been appropriately conducted and clearly described based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000)? Is the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR of 10% extra risk of the incidence of litters with any fetal skeletal anomalies) 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 appropriate based on the recommendations described in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

(B) Inhalation reference concentration (RfC) for biphenyl

1. The draft Toxicological Review of Biphenyl did not derive an RfC. Has the justification for not deriving an RfC been clearly described in the document? Are there available data to support the derivation of an RfC for biphenyl? If so, please identify these data.

(C) Carcinogenicity of biphenyl

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft Toxicological Review of Biphenyl concludes that the database for biphenyl provides "suggestive evidence of carcinogenic potential" by all routes of exposure. Please comment on whether this characterization of the human cancer potential of biphenyl is scientifically supported and clearly described.

2. EPA has concluded that biphenyl-induced urinary bladder tumors in male rats is a high-dose phenomenon involving sustained occurrence of calculi in the urinary bladder leading to transitional cell damage, sustained regenerative cell proliferation, and eventual promotion of spontaneously initiated tumor cells in the urinary bladder epithelium. Please comment on whether this determination is scientifically supported and clearly described. Please comment on data available that may support an alternative mode of action for biphenyl-induced urinary bladder tumors.

3. EPA has concluded that there is insufficient information to identify the mode(s) of carcinogenic action for biphenyl-induced liver tumors in mice. Please comment on whether this determination is appropriate and clearly described. If it is judged that a mode of action can be established for biphenyl-induced mouse liver tumors, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

Oral Slope Factor (OSF)

4. A two-year cancer bioassay of biphenyl in BDF_1 mice (Umeda et al., 2005) was selected as

the basis for the derivation of the OSF. Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the OSF, please indentify this study and provide scientific support for this choice.

5. The incidence of liver tumors (i.e., adenomas or carcinomas) in female mice was selected to serve as the basis for the derivation of the OSF. Please comment on whether this selection is scientifically supported and clearly described. If a different cancer endpoint is recommended for deriving the OSF, please identify this endpoint and provide scientific support for this choice.

6. Benchmark dose (BMD) modeling was conducted using the incidence of liver tumors in female mice in conjunction with dosimetric adjustments for calculating the human equivalent dose (HED) to estimate the point of departure (POD). A linear low-dose extrapolation from this POD was performed to derive the OSF. Has the modeling been appropriately conducted and clearly described based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000)? Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR of 10% extra risk of the incidence of liver tumors in female mice) been supported and clearly described?

7. EPA has concluded that a nonlinear approach is appropriate for extrapolating cancer risk from male rats to humans because the mode of action analysis suggests that rat bladder tumors occur only after a series of events that begin with calculi formation. At exposure levels below the RfD (i.e., below exposure levels needed to form calculi), no increased risk of cancer is expected. Please comment on whether this approach is scientifically supported and clearly described. Please identify and provide the rationale for any other extrapolation approaches that should be selected.

Inhalation Unit Risk (IUR)

8. The draft Toxicological Review of Biphenyl did not derive an IUR due to the lack of available studies. Are there available data to support the derivation of an IUR for biphenyl? If so, please identify these data.