

Draft Charge to External Reviewers for the IRIS Toxicological Review of Biphenyl July 2011

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment 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). An existing IRIS assessment for biphenyl includes an oral reference dose (RfD) (posted on IRIS in 1989) and a cancer weight-of-evidence descriptor (posted in 1991).

The current draft health assessment includes an RfD and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of biphenyl. 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 be likely to make a significant impact on the conclusions of the Toxicological Review.

Chemical-Specific Charge Questions:

(A) Oral Reference Dose (RfD) for Biphenyl

1. A developmental 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 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. Developmental effects in Wistar rats (i.e., fetal skeletal anomalies) were selected as the critical effect for the RfD. EPA considers this effect to be adverse. Please comment on whether the characterization and 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. Benchmark dose (BMD) modeling was applied to the incidence of fetal skeletal anomalies in Wistar 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 10% extra risk of the incidence of fetal skeletal anomalies) 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 Biphenyl

1. An RfC was not derived for biphenyl. Has the scientific justification for not deriving an RfC been clearly described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study.

(C) Carcinogenicity of Biphenyl

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgrd.html), the database for biphenyl provides "suggestive evidence of carcinogenic potential" by all routes of exposure. Is the cancer weight of evidence characterization scientifically supported and clearly described?

2. EPA has proposed a mode of action (MOA) for biphenyl-induced urinary bladder tumors in male rats 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 analysis regarding the MOA for male rat urinary bladder tumors is scientifically supported and clearly described.

Oral Slope Factor (OSF)

3. A two-year bioassay of biphenyl in BDF1 mice (Umeda et al., 2005) 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 liver tumors 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 low-dose linear extrapolation from the POD (i.e., the lower 95% confidence limit on the dose associated with 10% extra risk of liver tumors). Has the modeling been appropriately conducted and clearly described?

6. Please comment on the choice of the nonlinear threshold approach for the quantitative assessment of the carcinogenic potential of biphenyl associated with male rat urinary bladder tumors. Please comment on whether this approach is scientifically supported and clearly described.

Inhalation Unit Risk (IUR)

7. An IUR was not derived due to the lack of available studies to characterize the carcinogenic potential of biphenyl administered via inhalation. Is the rationale for not deriving an IUR scientifically supported and clearly described? Please identify and provide the rationale for any studies that should be selected as the principal study.