Draft Charge to External Reviewers for the
Toxicological Review of Hexachloroethane
March 2010

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment for hexachloroethane 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 hexachloroethane was posted on the database in 1987.

The current draft health assessment includes a chronic reference dose (RfD), reference concentration (RfC), and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of hexachloroethane. Please provide detailed explanations for responses to the charge questions.

General Charge Questions:

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

2. Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review and should be considered in the assessment of the noncancer and cancer health effects of hexachloroethane.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for hexachloroethane

1. A 16-week dietary exposure study of hexachloroethane in F344 rats by Gorzinski et al. (1985) was selected as the basis for the derivation of the RfD. Kidney effects were observed in male rats in this study at doses below the range of exposure tested in the available chronic NTP (1989) study. Please comment on the scientific justification for the use of the subchronic Gorzinski et al. (1985) study as the principal study for the derivation of the RfD. Is the rationale for this selection scientifically justified and clearly described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. An increase in the incidence of nephrotoxicity as indicated by atrophy and degeneration of renal tubules in male rats (Gorzinski et al., 1985) was selected as the critical effect for the RfD. Please comment on whether the selection of this critical effect is scientifically justified and clearly described. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling was applied to the atrophy and degeneration of renal tubules data to derive the point of departure (POD) for the RfD. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., a 10% increased incidence of nephrotoxicity as indicated by atrophy and degeneration of renal tubules in male rats compared with controls) scientifically justified and clearly described. Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

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 justified and clearly described in the document? Please provide a detailed explanation. If changes to the selected UFs are proposed, please identify and provide a rationale.

(B) Inhalation reference concentration (RfC) for hexachloroethane

1. A 6-week inhalation exposure study in rats by Weeks et al. (1979) was selected as the basis for the derivation of the RfC for hexachloroethane. Please comment on whether the selection of this study as the principal study is scientifically justified. Is the rationale for this selection clearly described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Neurobehavioral effects in Sprague-Dawley rats (Weeks et al., 1979) were selected as the critical effect for the RfC. Please comment on whether the selection of this critical effect is scientifically justified and clearly described in the document. Please identify and provide the rationale for any other endpoints that should be considered in the selection of 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 justified and clearly described.

4. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfC. Are the UFs scientifically justified and clearly described in the document? Please provide a detailed explanation. If changes to the selected UFs are proposed, please identify and provide a rationale.

(C) Carcinogenicity of hexachloroethane

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that hexachloroethane is *likely to be carcinogenic to humans.* Is the cancer weight of evidence characterization scientifically justified and clearly described?

2. A two-year oral gavage cancer bioassay in F344 rats (NTP, 1989) was selected for the development of an oral slope factor. Please comment on whether the selection of this study for quantification is scientifically justified and clearly described. Please identify and provide the rationale for any other studies that should be considered.

3. EPA selected the renal tubule tumor data in male rats from the NTP (1989) two-year oral gavage cancer bioassay to serve as the basis for the quantitative cancer assessment for hexachloroethane. Please comment on whether the rationale for this selection has been scientifically justified and clearly described. Please identify and provide the rationale for any other endpoints that should be considered to serve as the basis for the quantitative cancer assessment.

4. EPA concluded that the mode of action for kidney tumors observed following oral exposure to HCE is unknown. An analysis of the mode of action data for kidney tumors is presented in the Toxicological Review. Based on this analysis, EPA determined that HCE-induced kidney tumors could not be attributed to the accumulation of a_{2u}-globulin. Please comment on the scientific support for these conclusions. Please comment on whether the analysis is scientifically justified and clearly described.

5. The oral cancer slope factor was calculated by linear extrapolation from the POD (lower 95% confidence limit on the dose associated with 10% extra risk for renal tumors in male rats). Has the modeling approach been appropriately conducted and clearly described?