### Charge to External Reviewers for the Toxicological Review of Hexachloroethane May 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 EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). An existing IRIS assessment for hexachloroethane, which includes a chronic oral reference dose (RfD) and a carcinogenicity assessment, was posted on IRIS in 1987.

The current draft health assessment includes a chronic oral RfD, chronic inhalation 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. 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 hazards?

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

### **Chemical-Specific Charge Questions:**

### (A) Chronic 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 clearly described? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. 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 selected as the critical effect.

3. Benchmark dose (BMD) modeling was applied to the atrophy and degeneration of renal tubules data in male 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% increase in the incidence of atrophy and degeneration of renal tubules) scientifically justified 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 justified and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

## (B) Chronic 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. Please comment on whether the selection of this study as the principal study is scientifically justified. Is the rationale for this selection clearly described? 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. 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 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? 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/backgrd.html), hexachloroethane is *likely to be carcinogenic to humans* by all routes of exposure. 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 derivation of an oral slope factor. Please comment on whether the selection of this study for quantitation is scientifically justified and clearly described. Please identify and provide the rationale for any other studies that should be selected.

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

4. EPA concluded that the mode of action for renal tubule tumors observed following oral exposure to hexachloroethane is unknown. An analysis of the mode of action data for renal tumors is presented in the Toxicological Review. Based on this analysis, EPA determined that hexachloroethane-induced renal tumors could not be attributed to the accumulation of  $\alpha_{2u}$ -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 (i.e., the 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?