

**Draft External Peer Review Charge for the IRIS Toxicological Review of 1,1,2,2-Tetrachloroethane  
September 2, 2009**

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of 1,1,2,2-tetrachloroethane 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 of 1,1,2,2-tetrachloroethane was posted to the database in 1987.

The current draft health assessment includes subchronic and chronic reference doses (RfDs) and a cancer oral slope factor as part of a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of 1,1,2,2-tetrachloroethane. Please provide detailed explanations for responses to the charge questions.

**(A) General Charge Questions:**

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazard?
2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of 1,1,2,2-tetrachloroethane.

**Chemical-Specific Charge Questions:**

**(B) Oral reference dose (RfD) for 1,1,2,2-tetrachloroethane**

1. Subchronic and chronic RfDs for 1,1,2,2-tetrachloroethane have been derived from a 13-week oral gavage study (NTP, 2004) in rats and mice. Please comment on whether the selection of this study as the principal study has been scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.
2. Increased relative liver weight was selected as the critical effect for the derivation of the subchronic and chronic RfDs. Please comment on whether the rationale for the selection of this critical effect has been scientifically justified. Please provide a detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.
3. Hepatocellular vacuolization was observed at the lowest dose in the principal study (NTP, 2004). This effect was not selected as the critical effect for the determination of the POD for derivation of the subchronic and chronic RfDs. Please comment on the rationale and justification for not selecting this endpoint as the critical effect.
4. The subchronic and chronic RfDs have been derived utilizing benchmark dose (BMD)

modeling to define the point of departure (POD). All available models were fit to the data in both rats and mice for increased absolute and relative liver weight, increased incidence of hepatocellular cytoplasmic vacuolization (rats only), increased levels of ALT, SDH, and bile acids, and decreased fetal body weight. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., one standard deviation from the control mean) scientifically justified? 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.

5. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfDs. For instance, are they scientifically justified? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s). Please comment specifically on the following uncertainty factor:
  - A database uncertainty factor of 3 was used to account for the lack of oral reproductive and developmental toxicity data for 1,1,2,2-tetrachloroethane. Please comment on whether the application of this uncertainty factor has been scientifically justified.

#### **(C) Inhalation reference concentration (RfC) for 1,1,2,2-tetrachloroethane**

1. An RfC for 1,1,2,2-tetrachloroethane has not been derived. Has the scientific justification for not deriving an RfC been described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study. Please identify and provide the rationale for any endpoints that should be considered in the selection of the critical effect.

#### **(D) Carcinogenicity of 1,1,2,2-tetrachloroethane**

1. Under EPA's 2005 *Guidelines for carcinogen risk assessment* ([www.epa.gov/iris/backgr-d.htm](http://www.epa.gov/iris/backgr-d.htm)), the Agency concluded that 1,1,2,2-tetrachloroethane is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of the evidence characterization. Is the cancer weight of evidence characterization scientifically justified?
2. A two-year oral gavage cancer bioassay (NCI, 1978) was selected as the principal study for the derivation of an oral slope factor. Please comment on the appropriateness of the selection of the principal study.
3. An increased incidence of hepatocellular carcinomas in B6C3F1 mice was used to estimate the oral cancer slope factor. Please comment on the scientific justification of this analysis. Has the BMD modeling been appropriately conducted?