

Draft Charge to External Reviewers for the IRIS Toxicological Review of 1,2,3-Trichloropropane

January 11, 2007

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of 1,2,3-trichloropropane that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is a database of EPA's scientific position on the human health effects that may result from exposure to various substances found in the environment. IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). There is currently no assessment on the IRIS database for the health effects associated with 1,2,3-trichloropropane exposure.

The draft health assessment includes a chronic Reference Dose (RfD) and Reference Concentration (RfC) and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of 1,2,3-trichloropropane. 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 accurately, clearly and objectively represented and 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 1,2,3-trichloropropane.
3. Please discuss research that you think would be likely to reduce uncertainty in the toxicity values for future assessments of 1,2,3-trichloropropane.
4. Please comment on the identification and characterization of sources of uncertainty in sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Chemical-Specific Charge Questions:

(B) Oral reference dose (RfD) for 1,2,3-trichloropropane

1. A chronic RfD for 1,2,3-trichloropropane has been derived from a 2-year oral gavage study (NTP, 1993) in rats and mice. Please comment on whether the selection of this study as the principal study has been scientifically justified. Has this study been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Increased liver weight was selected as the critical effect. Please comment on whether the rationale for the selection of this critical effect has been scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please provide detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect. Please comment on the use of increased absolute liver weight instead of relative liver weight to describe the liver weight change.
3. The chronic RfD has 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 absolute and relative kidney weight, fertility generating the 4th and 5th litter, and the number of live pups/litter in the 4th and 5th litters. Please provide comments with regards to whether BMD modeling is the best approach for determining the point of departure. Has the BMD modeling been appropriately conducted and adequately described? Is the benchmark response selected for use in deriving the POD scientifically justified and has it been transparently and objectively described? Please identify and provide rationale for any alternative approaches (including the selection of BMR, model, etc.) for the determination of the point of departure, and if such approaches are preferred to EPA's approach.
4. 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 and transparently and objectively described in the document?
5. Please comment on the transparency and scientific rationale and justification for the selection of the database uncertainty factor. Please comment on whether the application of the database uncertainty factor adequately represents the gap in oral reproductive and developmental toxicity data for 1,2,3-trichloropropane.

(C) Inhalation reference concentration (RfC) for 1,2,3-trichloropropane

1. A chronic RfC for 1,2,3-trichloropropane has been derived from the 13 week inhalation study (Johannsen et al., 1988) in rats. Please comment on whether the selection of this study as the principal study is scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.
2. Peribronchial lymphoid hyperplasia in the lungs of male rats was selected as the critical toxicological effect. Please comment on whether the selection of this critical effect has been scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please provide detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. The chronic RfC has been derived utilizing the NOAEL/LOAEL approach to define the point of departure. Please provide comments with regards to whether this is the best approach for determining the point of departure. Please identify and provide rationale for any alternative approaches (including the selection of BMR, model, etc.) for the determination of the point of departure, and if such approaches are preferred to EPA's approach.
4. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfCs. For instance, are they scientifically justified and transparently and objectively described in the document?
5. EPA concluded that a database uncertainty factor of 10 was appropriate for the derivation of the RfC to account for the lack of a two-generation reproductive toxicity study and a developmental toxicity study. Please comment on whether the selection of the database uncertainty factor for the RfC is scientifically justified and has been transparently and objectively described in the document.

(D) Carcinogenicity of 1,2,3-trichloropropane

1. Under the EPA's 2005 *Guidelines for carcinogen risk assessment* (www.epa.gov/iris/backgr-d.htm), 1,2,3-trichloropropane is *likely to be carcinogenic to humans*. Please comment on the cancer weight of the evidence characterization. Do the available data support the conclusion that 1,2,3-trichloropropane is a likely human carcinogen? Has the scientific justification for the weight of evidence characterization been sufficiently, transparently, and objectively described? Has the scientific justification for deriving a quantitative cancer assessment been transparently and objectively described?
2. Evidence indicating the mode of action of carcinogenicity of 1,2,3-trichloropropane was considered. The proposed mode of action includes bioactivation of 1,2,3-trichloropropane leading to the induction of mutations in cancer-related genes. A conclusion was reached that it is possible that this chemical is operating through a mutagenic mode of action, but the database contains limited evidence of in vivo mutagenic events that could lead to the observed cancer. Please comment on whether the weight of the scientific evidence supports this conclusion. Please comment on whether the rationale for this conclusion has been transparently and objectively described. Please comment on data available for 1,2,3-trichloropropane that may support an alternative mode of action.
3. A two-year oral gavage cancer bioassay (NTP, 1993) was selected as the principal study for the development of an oral slope factor (OSF). Please comment on the appropriateness of the selection of the principal study. Has the rationale for this choice been transparently and objectively described?
4. Data on tumors in multiple organs in F344 rats were used to estimate the oral cancer

slope factor. Please comment on the scientific justification and transparency of this analysis. Please comment on the combination of etiologically similar tumor types, benign and malignant tumors of the same cell type, for quantitative purposes. Please specifically comment on EPA's inclusion of the data on forestomach tumors for cancer quantitation in rats following the administration of 1,2,3-trichloropropane. Please comment on the estimation of a statistically appropriate upper bound on total risk (combined slope factor), which describes the risk of developing any combination of tumor types considered, and the quantitative process used to calculate the combined slope factor.