

Final Draft Charge to External Reviewers for the Toxicological Review of Trichloroacetic Acid
May, 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of trichloroacetic acid 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 assessment on the IRIS database for the health effects associated with trichloroacetic acid exposure does not provide an oral RfD or inhalation RfC assessment, or quantification for carcinogenicity.

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

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 trichloroacetic acid.
3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of trichloroacetic acid.
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:

(A) Oral Reference Dose (RfD) for Trichloroacetic Acid

1. A chronic RfD for trichloroacetic acid has been derived from a 60-week drinking water study in mice (DeAngelo et al., 2008). Please comment on whether the selection of DeAngelo et al. (2008) as the principal study is scientifically justified. Has this study been transparently and objectively described in the document? Has the rationale for this selection 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. Liver toxicity (hepatocellular necrosis) was selected as the most appropriate critical effect. Please comment on whether the selection of this critical effect is scientifically justified. Has the rationale for this selection been transparently and objectively described in the document? Please provide detailed explanation. Please comment on whether EPA's rationale regarding the adversity of the critical effect has been adequately and transparently described and is supported by the available data. 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 used to analyze liver and testicular effects in male mice exposed to trichloroacetic acid in the drinking water study by DeAngelo et al. (2008). Please provide comments with regard to whether BMD modeling is the best approach for determining the POD. Has the BMD modeling been appropriately conducted and objectively and transparently described? Is the benchmark response (BMR) selected for use in deriving the POD scientifically justified? Has it been transparently and objectively 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 selection of the uncertainty factors applied to the POD for the derivation of the RfD. For instance, are they scientifically justified and transparently and objectively described in the document? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s).

(B) Inhalation Reference Concentration (RfC) for Trichloroacetic Acid

1. An RfC was not derived for trichloroacetic acid. Do you agree that there are no data available for derivation of an RfC for trichloroacetic acid? Has the rationale and justification for not deriving an RfC for trichloroacetic acid been transparently described in the document

(C) Carcinogenicity of Trichloroacetic Acid

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that the weight of evidence descriptor for trichloroacetic acid is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the scientific justification for the cancer weight of evidence characterization. Has the scientific justification for the weight of evidence descriptor been sufficiently, transparently and objectively described?

2. Have the studies supporting the discussion of modes of action been clearly described?

3. EPA has concluded that the available data on the hypothesized PPAR α agonism-peroxisome proliferation mode of action are insufficient to support a determination that this mode of action is not relevant to humans. Has the rationale for this determination been transparently and objectively described in the document?

4. EPA has concluded that the available data support the conclusion that other modes of actions besides PPAR α -peroxisome proliferation may be contributing to the carcinogenicity of trichloroacetic acid. Has the rationale for this determination been transparently and objectively described in the document?

5. An estimate of cancer risk was quantified for trichloroacetic acid. Has the scientific justification for deriving a quantitative cancer assessment been transparently and objectively described? Have the appropriate studies been selected for quantification of the oral cancer oral slope factor

6. Is the method used to derive the cancer oral slope factor for trichloroacetic acid appropriate?