Charge to External Reviewers for the
IRIS Toxicological Review of Trichloroacetic Acid
September 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 reference dose (RfD) or inhalation reference concentration (RfC), or quantification for carcinogenicity.

The current draft health assessment includes an (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 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 trichloroacetic acid.

Chemical-Specific Charge Questions:

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

1. A 60-week drinking water study in mice (DeAngelo et al., 2008) was selected as the basis for derivation of the RfD for trichloroacetic acid. Please comment on whether the selection of DeAngelo et al. (2008) as the principal study is scientifically justified. 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 critical effect for the determination of the point of departure (POD). Please comment on whether the selection of this critical effect is scientifically justified. 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 conducted on the liver and testicular effects in male mice exposed to trichloroacetic acid in the drinking water study by DeAngelo et al. (2008) in order to determine the POD. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., 10% extra risk of hepatocellular necrosis) 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.

4. Please comment on the rationale for the selection of the uncertainty factors applied to the POD for the derivation of the RfD. 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. Has the scientific justification for not deriving an RfC been clearly described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study.

(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 trichloroacetic acid is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the weight of evidence characterization scientifically justified?

2. Have the studies supporting the discussion of the mode(s) of carcinogenic action been clearly described?

3. EPA has concluded that the available data do not support any specific mode of action. In addition, EPA has determined that the data are not supportive of PPARalpha agonist-induced peroxisome proliferation as the sole mode of action leading to tumor formation. Please comment on whether these determinations are scientifically justified.

4. A 104-week drinking water study in mice (DeAngelo et al., 2008) was selected as the basis for quantification of the oral cancer slope factor. Please comment on whether the selection of this study is scientifically justified.

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 liver tumors). Has the modeling approach been appropriately conducted? Please identify and provide the rationale for any alternative approaches for the determination of the slope factor and discuss whether such approaches are preferred to EPA's approach.

6. An inhalation unit risk (IUR) for cancer was not derived for trichloroacetic acid. Is the determination that the available data for trichloroacetic acid do not support derivation of an IUR scientifically justified?