Charge to External Reviewers for the
Toxicological Review of Thallium and Compounds
January 2008

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of thallium and compounds 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). Existing IRIS assessments of selected thallium compounds were posted to the database in 1987.

The draft health assessment includes a Reference Dose (RfD) and a carcinogenicity assessment. Below are a set of charge questions that address scientific issues in the assessment of thallium and compounds. Please provide detailed explanations for responses to the charge questions.

As the study used for the principal basis of the RfD (Midwest Research Institute [MRI], 1988) was not peer reviewed, EPA had an external review of the study conducted in 2006. To help inform your evaluation, EPA is also providing you with the external peer review report summary.

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 thallium and thallium compounds.

3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of thallium and compounds.

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 thallium

1. The 90-day oral gavage study by Midwest Research Institute (MRI, 1988) was selected as the basis for the RfD. 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. Alopecia (hair loss) was selected as the most appropriate critical effect for the RfD. EPA characterizes alopecia as being an adverse effect. Please comment on whether the science and mode of action information supports alopecia as an adverse effect. EPA has stated: "Whether alopecia is itself an adverse effect merits consideration. In humans, alopecia is generally reversible upon cessation of thallium exposure. Alopecia, however, appears to be a part of a continuum of dermal changes observed following thallium exposure, as well as one of a spectrum of effects on target organs that include the nervous and gastrointestinal systems. For these reasons, alopecia supported by two cases of hair follicle atrophy is considered an adverse effect." Please comment on whether the selection of this critical effect has been scientifically justified. Is EPA's choice transparently and objectively described in the document? Please provide a detailed explanation. Please identify and provide the rationale for any other endpoints that should be used instead of alopecia to develop the RfD.

3. At the high dose in the MRI (1988) study, two female rats exhibited moderate to severe alopecia that could not be attributed to self-barbering or normal cyclic hair growth. Histologic examination of skin samples from these high-dose females showed atrophy of hair follicles. EPA considered these findings to be adverse, and thus the high dose in this study (0.25 mg/kg-day thallium sulfate) to be the lowest-observed-adverse-effect level (LOAEL). The mid-dose group (0.05 mg/kg-day thallium sulfate) was identified as the no-observed-adverse-effect level (NOAEL). Is EPA's interpretation of the study findings scientifically justified? Has this interpretation of the findings been transparently and objectively described in the document?

   As part of the evaluation of alopecia as a critical effect for the RfD, EPA performed a series of Fisher's Exact Tests to determine if the incidence of alopecia in any of the three dose groups was statistically significantly elevated above controls using all cases of alopecia reported by MRI (1988). Please comment on whether EPA chose the appropriate data set and the appropriate statistical test for this analysis.

   The study investigators reached a different interpretation of the study findings than did EPA. The investigators considered alopecia to be attributable to the cyclic pattern of hair growth in rodents and, consequently, did not consider these findings to be biologically significant. The high dose (0.25 mg/kg-day thallium sulfate) was identified in MRI (1988) as the NOAEL. Is the study authors' conclusion that the high dose (0.25 mg/kg-day thallium sulfate) represents a NOAEL justified and supported by the study data?

4. The traditional NOAEL-LOAEL approach was used to define the point of departure (POD) for the RfD. A benchmark dose (BMD) analysis was considered but was not conducted because of the nature of the data set for alopecia. Please provide comments with regards to whether a NOAEL-LOAEL approach is the best approach for determining the POD. Has the approach been scientifically justified? Is it transparently and objectively described? Please identify and provide a rationale for any alternative approaches for the determination of the POD, and if 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 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).

6. Please comment specifically on the database uncertainty factor of 10 applied in the RfD derivation. Please comment on the use of the database uncertainty factor specifically for the lack of adequate developmental toxicity studies and a two-generation reproductive toxicity study, and additional uncertainty associated with the limited data available on neurotoxicity in light of the potential for neurotoxicity to represent a sensitive endpoint for thallium exposure. Please comment on whether the selection of the database uncertainty factor for the RfD has been scientifically justified. Has this selection been transparently and objectively described in the document?

(B) Inhalation reference concentration (RfC) for thallium and compounds

No data are available to derive the RfC for thallium and compounds. The only published studies involving inhalation exposure include a few case reports (Hirata et al., 1998; Ludolph et al., 1986) that suggest an association between occupational exposure and toxicity (including alopecia, gastrointestinal symptoms, and neuropathy), but the route or routes of exposure in these workplace setting could not be established.

1. Has the rationale and justification for not deriving an RfC for thallium been transparently described in the document?

(C) Carcinogenicity of thallium and compounds

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that there is *inadequate information to assess the carcinogenic potential* of thallium and compounds. Please comment on the scientific justification for the cancer weight of the evidence characterization. A quantitative cancer assessment was not derived for thallium. Has the scientific justification for not deriving a quantitative cancer assessment been transparently and objectively described?