

## **Draft Charge to External Reviewers for the IRIS Toxicological Review of Cerium Oxide and Cerium Compounds**

**May 1, 2008**

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of cerium oxide and cerium 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). There is currently no assessment on the IRIS database for the health effects associated with cerium compound exposure.

The draft health assessment includes a chronic Reference Concentration (RfC). Below is a set of charge questions that address scientific issues in the assessment of cerium oxide and cerium compounds. 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 cerium oxide and cerium compounds.
3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of cerium oxide.
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 cerium**

1. A chronic RfD for cerium compounds has not been derived. Has the scientific justification for not deriving an RfD been transparently and objectively described? 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.

#### **(C) Inhalation reference concentration (RfC) for cerium**

1. A chronic RfC for cerium oxide has been derived from the 13 week inhalation study (BRL, 1994) in rats. 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? Are the criteria and rationale for the selection of this study 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 incidence of lymphoid hyperplasia in the bronchial lymph nodes of male rats was selected as the critical toxicological effect. The selection of increased incidence of lymphoid hyperplasia in the bronchial lymph nodes as the critical effect for cerium oxide is because it is considered by EPA to be a precursor to an adverse effect. Please comment on whether the selection of this critical effect has been scientifically justified. Are the criteria and rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please comment on whether EPA's rationale about 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 used instead of lymphoid hyperplasia to develop the RfC.
3. Some mode of action evidence exists suggesting that lymphoid hyperplasia in the bronchial lymph nodes represents a sensitive endpoint that occurs early in a series of critical events leading to more severe effects in the lung. Specifically, the data suggest that lymphoid hyperplasia in the bronchial lymph nodes may represent the point at which normal clearance of particles from the lung by alveolar macrophages becomes overwhelmed and particles are no longer cleared effectively. This delayed clearance leads to increased accumulation of cerium oxide particles in the respiratory tract, an inflammatory response, and subsequent cell proliferation. Please comment on whether the available mode of action data supports this proposed MOA for cerium oxide-induced bronchial lymphoid hyperplasia. Is this proposed MOA scientifically justified and transparently and objectively described?
4. 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 for the determination of the point of departure, 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 RfC. For instance, are they scientifically justified and transparently and objectively described in the document?
6. Please comment on the transparency, scientific rationale and justification for the LOAEL-to-NOAEL uncertainty factor of 3. Are the criteria and rationale for this selection transparently and objectively described in the document? The point of departure for this analysis was based on the critical effect of lymphoid hyperplasia in

the bronchial lymph nodes. This effect is described as a sensitive effect occurring early in the series of critical events leading to more severe effects in the lung, and hence a default 10-fold uncertainty factor was not applied. The mode of action for the critical effect is thought to be related to pulmonary clearance overload, in which normal clearance of particles from the lung by alveolar macrophages becomes overwhelmed and particles are no longer cleared effectively, leading to an increasing accumulation of particles in the lung and airways, an inflammatory response, and subsequent cell proliferation. Please comment on whether the justification for selection of the LOAEL-to-NOAEL uncertainty factor based on these data is scientifically justified and transparently described.

7. Please comment on the transparency, scientific rationale and justification for the selection of the database uncertainty factor. Please comment on whether the application of the database uncertainty factor adequately addresses the lack toxicity data for cerium oxide. Specifically, please comment on whether studies addressing additional endpoints of concern (e.g. reproductive and developmental toxicity studies) would likely result in a lower point of departure. Are the criteria and rationale for this selection transparently and objectively described in the document? An uncertainty factor of 3 was applied with special consideration of the information pertaining to the deposition and absorption of cerium oxide, the effects observed in humans following prolonged exposure, the mode of action data, and the similar effects observed in animals in the principal study.
8. The RfC has been derived using data from inhalation exposure to cerium oxide (BRL, 1994). Is the statement to not use the RfC for cerium compounds other than cerium oxide scientifically justified? Is there enough information on and discussion of cerium compounds to warrant the title "cerium oxide and cerium compounds"?

#### **(D) Carcinogenicity of cerium**

1. Under the EPA's 2005 *Guidelines for carcinogen risk assessment* ([www.epa.gov/iris/backgr-d.htm](http://www.epa.gov/iris/backgr-d.htm)), there is "*inadequate information to assess the carcinogenic potential*" of cerium compounds. Please comment on the scientific justification for the cancer weight of the evidence characterization. Has the scientific justification for the weight of evidence characterization been sufficiently, transparently, and objectively described? Has the scientific justification for not deriving a quantitative risk estimate been transparently and objectively described?