Charge to External Reviewers for the
Toxicological Review of Halogenated Platinum Salts and Platinum Compounds
January 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of halogenated platinum salts and platinum 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). Currently an IRIS assessment of halogenated platinum salts and platinum compounds does not exist on the database.

The current draft health assessment includes a chronic reference concentration (RfC). Below is a set of charge questions that address scientific issues in the assessment of halogenated platinum salts and platinum compounds. 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 hazards?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of halogenated platinum salts and platinum compounds.

3. Please discuss research that you think would be likely to reduce uncertainty in future assessments of halogenated platinum salts and platinum 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 halogenated platinum salts and platinum compounds

1. An RfD was not derived due to lack of adequate data to characterize the health effects associated with oral exposure to halogenated platinum salts and platinum compounds. Are you aware of any data that might support development of an RfD for halogenated platinum salts and platinum compounds?

(B) Inhalation reference concentration (RfC) for halogenated platinum salts and platinum compounds

1. The Merget et al. (2000) occupational epidemiological study was selected as the basis for the RfC. Please provide a detailed explanation of any strengths or weaknesses regarding the Merget et al. (2000) study that are not identified or adequately reviewed in the current assessment. Please comment on whether the selection of this study as the principal study is scientifically justified. 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. Pt-specific allergic sensitization, as measured by the development of a positive skin prick test (SPT), was selected as the critical effect for the RfC resulting from exposure to halogenated platinum salts. Please comment on whether the selection of this critical effect is scientifically justified. Is the rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please comment on EPA's rationale regarding adversity of the critical effect. Has it been objectively and transparently described and is it supported by the available data and your understanding of the available scientific data. Please identify and provide the rationales for any other endpoints that should be considered in the selection of the critical effect.

3. The RfC was quantified for halogenated Pt salts from the Merget et al. (2000) occupational epidemiological study which provided exposure data from airborne soluble Pt measurements that were not further characterized for specific Pt compounds. Please comment on the scientific justification of the derivation of an RfC for halogenated Pt salts from measurements of airborne soluble Pt that were not further characterized for specific Pt compounds. Please identify and provide the rationale for any other approaches that should be considered in the derivation of an RfC for Pt compounds.

4. Is the statement that "The use of the RfC for Pt compounds other than halogenated Pt salts is not recommended as the similarity between these compounds and other soluble forms of Pt compounds is unknown" scientifically justified? Please identify and provide the rationale for any other characterization of the platinum compounds that are relevant to the recommended use of the RfC.

5. EPA has concluded that the allergenic activity of Pt is compound-dependent and sensitization effects appear to be restricted to the halogenated Pt salts. Please comment on whether this finding is justified and supported by the scientific evidence.

6. The Merget et al. (2000) study reported 13/115 workers in the high exposure group developed Pt-specific allergic sensitization (as determined by a positive SPT) during the 5-year study period. The Merget et al. (2000) study did not adjust its reporting of SPT positive individuals for smoking as a risk factor for developing Pt-specific allergic sensitization. Please provide comments on the potential impact of this approach and implications it may have for the RfC derived from this study.

7. The RfC was derived on the basis that chronic exposure at the dose level would not induce allergic sensitization. However, it is unknown if the RfC would be protective of exacerbation of symptoms in individuals previously sensitized to halogenated platinum salts. Please comment on whether the decision not to derive an RfC based upon elicitation of an allergic response as the critical effect is scientifically sound and has been transparently and objectively described in the document.

8. A NOAEL/LOAEL approach was applied to incidence data for Pt-specific allergic sensitization to derive the POD for the RfC. The available data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) are available and only one of these groups has a non-zero response. However, BMD modeling was applied to incidence data for Pt-specific allergic sensitization for comparative purposes. Please provide comments with regard to whether the NOAEL approach is the best approach for determining the POD. Have the NOAEL approach and the BMD modeling approach been appropriately conducted and objectively and transparently described? Please identify and provide rationales for any alternative approaches (including BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

9. Insufficient information is available to predict potential variability in susceptibility among the general population to allergic sensitization from inhaled halogenated Pt salts. Please comment on the transparency, scientific rationale and justification for the use of an uncertainty factor of 10 to account for interindividual variability. Are the criteria and rationale for this selection transparently and objectively described in the document? Please comment on whether the justification for selection of this uncertainty factor based on these data is scientifically justified and transparently described.

10. A subchronic study (Merget et al., 2000) was selected as the principal study with allergic sensitization to halogenated Pt salts as the critical effect for the derivation of the RfC. Please comment on the transparency, scientific rationale and justification for the subchronic to chronic uncertainty factor of 10. Are the criteria and rationale for this selection transparently and objectively described in the document?

11. An uncertainty factor of 10 was used to account for deficiencies in the halogenated platinum salts and platinum compounds database. The inhalation database currently does not include a chronic, developmental, or a two-generation reproductive toxicity study. Overall, the basic toxicology of halogenated platinum salts and platinum compounds has not been well characterized. 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 halogenated platinum salts and platinum compounds. Are the criteria and rationale for this selection transparently and objectively described in the document?

(C) Carcinogenicity of halogenated platinum salts and platinum 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 evidence to determine the carcinogenic potential* of halogenated platinum salts and platinum compounds. Please comment on the cancer weight of evidence characterization. Does the lack of available data support the conclusion that there is *inadequate evidence to determine the carcinogenic potential* halogenated platinum salts and platinum compounds? Has this recommendation been transparently and objectively described in the document?