Final Draft Charge to External Reviewers for the Toxicological Review of Bromobenzene
June 7, 2007

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of bromobenzene that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is a database of EPA's scientific position on the human health effects that may result from exposure to various substances found in the environment. There is currently no assessment on the IRIS database for the health effects associated with bromobenzene exposure.

The draft health assessment includes chronic and subchronic Reference Doses (RfD) and Reference Concentrations (RfC) and a carcinogenicity assessment. Below are a set of charge questions that address scientific issues in the assessment of bromobenzene. 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 bromobenzene.

Chemical-Specific Charge Questions:

(B) Oral reference dose (RfD) for bromobenzene

1. A subchronic and chronic RfD for bromobenzene have been derived from the 90-day oral gavage study (NTP, 1985b) in mice. Please comment on whether the selection of this study as the principal study has been scientifically justified and 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 (including increased liver weight and liver lesions) was selected as the most appropriate critical effect. Please comment on whether the selection of this critical effect has been scientifically justified and transparently and objectively described in the document. Please provide detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. The subchronic and chronic RfDs have been derived utilizing benchmark dose (BMD) modeling to define the point of departure (POD). All available models were fit to the data for the combined incidence of animals with one or more of the histopathologic liver lesions (centrilobular cytomegaly, necrosis, inflammation, mineralization), liver weight, and SDH levels. Please comment on the

appropriateness and scientific justification presented for combining the incidence of liver effects to obtain a data set for BMD modeling. Please provide comments with regards to whether BMD modeling is the best approach for determining the point of departure. Has the BMD modeling been appropriately conducted and objectively and transparently described? Has the benchmark response selected for use in deriving the POD been scientifically justified and transparently and objectively described? Please comment on the appropriateness of averaging the benchmark doses for increased liver weight and liver lesions to derive the POD. Please identify and provide rationale for any alternative approaches (including the selection of BMR, model, etc.) for the determination of the point of departure, and if 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 RfDs. For instance, are they scientifically justified and transparently and objectively described in the document?

5. EPA used the data available for chlorobenzene to inform the selection of the subchronic to chronic uncertainty factor for the derivation of the chronic RfD for bromobenzene. Please comment on the scientific justification for this use of data from chlorobenzene. Has the scientific justification for this selection been transparently and objectively presented?

(C) Inhalation reference concentration (RfC) for bromobenzene

1. A subchronic and chronic RfC for bromobenzene has been derived from the 13 week inhalation study (NTP, 1985d) in mice. Please comment on whether the selection of this study as the principal study has been scientifically justified and 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 cytomegaly in female mice was selected as the critical toxicological effect. Please comment on whether the selection of this critical effect has been scientifically justified and transparently and objectively described in the document. Specifically, please address whether the selection of increased incidence of cytomegaly as the critical effect instead of increased liver weight has been adequately and transparently described. Please provide detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. The subchronic and chronic RfCs have been derived utilizing benchmark dose modeling to define the point of departure. Please provide comments with regards to whether BMD modeling is the best approach for determining the point of departure. Has the BMD modeling been appropriately conducted and objectively and transparently described? Has the benchmark response selected for use in deriving the POD been scientifically justified and transparently and objectively described? Please comment on the justification for not utilizing the 100 ppm dose identified in

the NTP (1985d) study as a NOAEL. Please identify and provide rationale for any alternative approaches (including the selection of BMR, model, etc.) for the determination of the point of departure, and if 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 RfCs. For instance, are they scientifically justified and transparently and objectively described in the document.

5. EPA used the data available for chlorobenzene to inform the selection the subchronic to chronic uncertainty factor for the derivation of the chronic RfC for bromobenzene. Please comment on the scientific justification for this use of data from chlorobenzene. Has the scientific justification for this selection been transparently and objectively presented?

(D) Carcinogenicity of bromobenzene

1. Under the EPA's 2005 *Guidelines for carcinogen risk assessment* (www.epa.gov/iris/backgr-d.htm), *data are inadequate for an assessment of the human carcinogenic potential* of bromobenzene. Please comment on the scientific justification for the cancer weight of the evidence characterization. A quantitative cancer assessment was not derived for bromobenzene. Has the scientific justification for not deriving a quantitative cancer assessment been transparently and objectively described?