**Draft Charge to External Reviewers for the Toxicological Review of Tetrahydrofuran
August 8, 2007**

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of tetrahydrofuran (THF) 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 THF exposure.

The draft health assessment includes chronic 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 THF. 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 THF.

Chemical-Specific Charge Questions:

(B) Oral reference dose (RfD) for Tetrahydrofuran

1. A chronic RfD for THF has been derived from the oral drinking water 2-generation reproductive toxicity study (BASF, 1996; Hellwig et al., 2002) in rats. 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. Decreased F2 male pup body weight 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 chronic RfD has been derived utilizing benchmark dose (BMD) modeling to

define the point of departure (POD). All available models were fit to the individual male and female and combined incidence data (F1 and F2 pup body weight gain). Please comment on the appropriateness and scientific justification presented for individual and combined body weights 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 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 RfD. For instance, are they scientifically justified and transparently and objectively described in the document?

5. A two-generation reproductive toxicity study was used for the selection of the POD for the derivation of the RfD. Please comment on whether the rationale and justification for not applying a subchronic to chronic uncertainty factor has been scientifically justified and transparently described in the document.

6. Please comment on whether the rationale and justification for the selection of the database uncertainty factor has been scientifically justified and transparently described in the document.

(C) Inhalation reference concentration (RfC) for Tetrahydrofuran

1. A chronic RfC for THF has been derived from data from a 105 week chronic inhalation study (NTP, 1998) in mice and rats. 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 and CNS effects were selected as the co-critical toxicological effects. 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 liver effects and CNS toxicity as the co-critical effects instead of increased thymus weight has been adequately and transparently described. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. The chronic RfC has been derived utilizing benchmark dose modeling to define the point of departure (based on liver cytomegaly). BMD modeling was conducted on liver weight and cytomegaly data in both males and females. 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 provide comments on whether the selection of a POD based on liver cytomegaly instead of liver weight is scientifically justified and transparently described. 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. No incidence data were presented for CNS effects. Thus, these data could not be evaluated by BMD modeling. However, a NOAEL LOAEL approach (based on the CNS data) for the derivation of the RfC has been presented for comparison purposes. Please provide comments as to whether the NOAEL LOAEL approach based on the POD for CNS effects is more appropriate for the derivation of the RfC. Please provide comments with regards to whether BMD modeling is the best approach for determining the point of departure.

5. Please comment on whether 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.

6. Please comment on the transparency and scientific rationale and justification for the selection of the database uncertainty factor. Please comment on whether the application of the database uncertainty factor adequately represents the gap in inhalation reproductive and developmental toxicity and immunotoxicity data for THF. Please comment on whether the rationale for use of the oral data to inform this decision scientifically justifiable and transparently described in the document.

7. THF induces a spectrum of effects consistent with both Category 1 and Category 3 gases. Therefore, for the purposes of calculating human equivalent concentrations, respiratory tract effect levels were calculated using the default equations for Category 1 gases and extrarespiratory tract effect levels were calculated using default equations for Category 3 gases. Please comment on the explanation for the dosimetry choice in the derivation of the RfC. Has the rationale been scientifically justified and transparently described?

(C) Carcinogenicity of Tetrahydrofuran

1. Under the EPA's 2005 *Guidelines for carcinogen risk assessment* (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283), there is *suggestive evidence for the human carcinogenic potential* of THF. Please comment on the scientific justification for the cancer weight of the evidence characterization. A quantitative cancer assessment has been derived for THF. Do the data support estimation of a cancer slope factor for THF? Please comment on the scientific justification for deriving a quantitative cancer assessment considering the uncertainty

in the data and the suggestive nature of the weight of the evidence of carcinogenic potential. Has the rationale and scientific justification for quantitation been transparently and objectively described?

2. The available data suggest that a plausible mode of action for THF-induced male rat kidney tumors may involve the accumulation of alpha-2u globulin. EPA concluded that the available data do not provide significant biological support to establish a mode of action for male rat kidney tumors and that these tumors are relevant to humans. Please comment on the transparency and scientific rationale and justification for the evaluation of these data and the conclusions regarding the possible mode(s) of action and human relevance for the male rat kidney tumors.

3. The available data suggest that increased proliferation and promotion in the liver may be a plausible mode of action for THF-induced female mouse liver tumors. EPA concluded that the data do not provide significant biological support to establish a mode of action for female mouse liver tumors and that these tumors are relevant to humans. Please comment on the transparency and scientific rationale and justification for the evaluation of these data and the conclusions regarding the possible mode(s) of action and human relevance for the female mouse liver tumors.

4. An inhalation unit risk has been derived utilizing benchmark dose modeling to define the point of departure of 10% extra risk followed by linear low-dose extrapolation below the point of departure (i.e., the default assumption). Please comment on the scientific justification and rationale supporting the estimation of an inhalation unit risk from the available data for THF. Specifically, please comment on whether the rationale for the quantitative analysis is objectively and transparently described, considering the uncertainty in the data and the suggestive nature of the weight of evidence. Please comment on the selection of linear low dose extrapolation. Has the justification of linear low dose extrapolation been objectively and transparently presented? Please identify and provide rationale for any alternative approaches for low dose extrapolation that the data for THF would support and if such approaches are preferred to EPA's approach.

5. THF induces a spectrum of effects consistent with both Category 1 and Category 3 gases. Therefore, for the purposes of calculating human equivalent concentrations, respiratory tract effect levels were calculated using the default equations for Category 1 gases and extrarespiratory tract effect levels were calculated using default equations for Category 3 gases. Please comment on the explanation for the dosimetry choice in the derivation of the inhalation unit risk. Has the rationale been scientifically justified and transparently described?