

**Charge to External Reviewers for the
IRIS Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE)
July 2009**

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of ethyl tertiary butyl ether (ETBE) 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 ETBE does not exist on the database.

The current draft health assessment includes a chronic reference concentration (RfC), and a qualitative carcinogenicity assessment. A reference dose (RfD) could not be derived, however, an oral value for limited purposes, such as for screening level risk assessments, is included in Appendix C. Below is a set of charge questions that address scientific issues in the assessment of ETBE. Please provide detailed explanations for responses to the charge questions.

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly 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 ETBE.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for ETBE

Upon evaluation of the oral database, EPA determined that it was not possible to derive an oral RfD as the proposed composite uncertainty factor (UF) of 10,000 would lead to a value with an unacceptable level of uncertainty (see *A Review of the Reference Dose and Reference Concentration Processes*, U.S. EPA, 2002 for discussion of UFs). In lieu of deriving an RfD, the available data were used to derive an oral value (i.e., a minimal data value) for limited risk assessment purposes as discussed in Appendix C.

1. The CIT (2004b) two-generation study of reproduction and fertility effects of oral exposure to ETBE was selected as the basis for the derivation of the minimal data value. Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.
2. Increased kidney weight in F0 generation male rats (CIT, 2004b) was selected as the critical effect for the minimal data value resulting from oral exposure to ETBE. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling methods were applied to kidney weight data to derive the point of departure (POD) for the minimal data value. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., one standard deviation from the control mean) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. A total composite UF of 10,000 was used to derive a minimal data value for ETBE. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the minimal data value. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(B) Inhalation reference concentration (RfC) for ETBE

1. The Medinsky et al. (1999) 13-week inhalation exposure study in mice and rats was selected as the basis for derivation of the RfC for ETBE. Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. The occurrence of regenerative foci in the kidneys of male rats (Medinsky et al., 1999) was selected as the critical effect for the RfC. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. An analysis of the mode of action of kidney effects is presented in the Toxicological Review and a determination is made that the mode of action in male and female rats is unknown. Please comment on whether the analysis is scientifically justified.

4. BMD modeling was applied to data for the mean number of regenerative foci in the kidneys to derive the POD for the RfC. Has the BMD modeling been appropriately conducted? Has the BMR selected for use in deriving the POD (i.e., one standard deviation from the control mean) been scientifically justified? Please identify and provide the rationale 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.

5. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfC. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(C) Carcinogenicity of ETBE

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that there is *suggestive evidence of carcinogenic potential* following oral exposure to ETBE. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified?

2. EPA did not derive a quantitative estimate of the carcinogenic potential of ETBE. Do the data support an estimation of a cancer slope factor for ETBE? If a quantitative estimate is proposed, please identify and provide a detailed description of the method(s) and approach(es) for deriving a cancer slope factor.