

**Draft Charge to External Peer Reviewers for the
IRIS Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE)
April 11, 2008**

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

An IRIS assessment for EGBE was posted to the database in 1999. The current draft health assessment includes a chronic Reference Dose (RfD) and Reference Concentration (RfC), and a carcinogenicity assessment. In 2005 EPA released "[An Evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl Ether](#)" (EPA/600/R-04/123) (available at <<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=135268>>). External peer review comments and EPA's disposition are available as an Appendix to the 2005 EPA document. This document formed the basis, in part, of the external review draft IRIS assessment.

Below is a set of charge questions that address scientific issues in the assessment of EGBE. Please provide detailed explanations for responses to the charge questions.

General Charge Questions:

1. Is the Toxicological Review logical and clear? 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 EGBE.
3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of EGBE.
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) Inhalation reference concentration (RfC) for EGBE

1. The 2-year inhalation study by the National Toxicology Program (NTP, 2000) was selected as the basis for the chronic inhalation RfC. 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? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. The incidence of hemosiderin staining in the liver of male rats was selected as the critical effect 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 discussion. 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 was applied to incidence data for hemosiderin staining in male rat liver to derive the point of departure (POD) for the RfC. Please provide comments with regard to whether BMD modeling is the best approach for determining the POD. Has the BMD modeling been appropriately conducted and objectively and transparently described? Has the benchmark response (BMR) selected for use in deriving the POD (i.e., 10% extra risk of hemosiderin staining in the liver) been scientifically justified, and transparently and objectively described? Please identify and provide the rationale for any alternative approaches for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. PBPK modeling was used to extrapolate the POD from rats to humans. Please comment on whether the PBPK modeling for interspecies extrapolation is scientifically justified, and transparently and objectively described in the document. Does the model properly represent the toxicokinetics of the species under consideration? Was the model applied properly? Are the model assumptions, parameter values, and selection of dose metrics clearly presented and scientifically supported?

5. Please comment on the selection of all of the uncertainty factors applied to the POD for the derivation of the chronic RfC. For instance, are they scientifically justified, and transparently and objectively described in the document? An UF of 10 for extrapolation from animals to humans (UF_A) is generally applied when data are not available to inform potential pharmacokinetic (PK-UF) and pharmacodynamic (PD-UF) differences. In this assessment, an UF_A of 1 was applied.

- A PBPK model was used to inform pharmacokinetic differences and a PK-UF of 1 was selected. Please comment on whether this selection is scientifically justified. Is the rationale transparently and objectively described? Please comment on whether there are sufficient scientific data and support for the use of this PBPK model to estimate interspecies toxicokinetic differences and to replace the default interspecies factor for toxicokinetic differences (i.e., $10^{1/2}$).
- Evidence from human and animal in vitro and in vivo studies was used to inform pharmacodynamic differences and a PD-UF of 1 was selected. Please comment on whether this selection is scientifically justified. Is the rationale transparently and objectively described? Please comment on whether a higher value for the PD-UF should be used (e.g., to account for the limited information available on the potential for effects in human cell types other than red blood cells) or alternatively, should a lower (i.e., fractional) PD-UF be used (e.g., to account for the 40 - 150 fold difference in the concentrations that cause pre-hemolytic effects in human red blood cells (RBCs),

including RBCs from potential susceptible populations such as the elderly, and patients suffering from anemia and RBC disorders that weaken the cellular membrane such as hereditary spherocytosis).

Please identify and provide the rationale for any alternative approaches for the selection of the uncertainty factors.

6. Please comment specifically on the database uncertainty factor of 1 applied in the RfC derivation. Are the criteria and rationale for the selection of the database uncertainty factor transparently and objectively described in the document? Please comment on the body of information regarding the hemato and hepatic toxicity of EGBE and the use of the toxicokinetic data in the determination of the database uncertainty factor. Please comment on whether the selection of the database uncertainty factor for the RfC has been scientifically justified. Has this selection been transparently and objectively described in the document?

(B) Oral reference dose (RfD) for EGBE

1. A conclusion was reached that the available oral toxicity data are inadequate to support derivation of a chronic oral RfD value. Is the rationale for not developing an RfD from the available database of oral studies transparently and objectively described? If other oral studies are identified that would be suitable for the derivation of the RfD, please identify and provide the rationale for their use.

2. A route-to-route extrapolation was performed to derive the chronic RfD, using the chronic inhalation study and PBPK modeling. The Human Equivalent Concentration (HEC) was based on a continuous oral exposure to EGBE in drinking water that would yield the same AUC for the metabolite BAA (in the arterial blood over three months) as that estimated for the rat following an external inhalation exposure to EGBE at the level of the proposed POD (i.e., the BMCL₁₀). Please comment on whether the PBPK model is adequate for use to conduct a route-to-route extrapolation for EGBE to derive an RfD in the absence of adequate oral animal or human dose-response data to derive the RfD directly. Was the extrapolation correctly performed and objectively and transparently documented?

3. Please comment specifically on the database uncertainty factor of 1 applied in the RfD derivation. Are the criteria and rationale for the selection of the database uncertainty factor transparently and objectively described in the document? Measured internal doses in rats and a human PBPK model were used to perform a route-to-route extrapolation to derive the RfD. Please comment on the use of the PBPK model and the inhalation database in the determination of the database uncertainty factor for the RfD. Please comment on whether the selection of the database uncertainty factor for the RfD has been scientifically justified. Has this selection been transparently and objectively described in the document?

(C) Carcinogenicity of EGBE

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/background.htm), the Agency concluded that EGBE is *not likely to be*

carcinogenic to humans at expected exposure concentrations. Please comment on the scientific justification for the cancer weight of evidence characterization and describe the basis for your view. Has the scientific justification for the weight of evidence descriptor been sufficiently, transparently and objectively described?

2. EPA has proposed a mode of action (MOA) for male mouse liver cancer involving metabolism, hemolysis of RBCs, hemosiderin deposition in the liver, oxidative damage and proliferation leading to tumor induction as key events best supported by the data. Please provide detailed comments on whether this analysis regarding the MOA for liver cancer is scientifically sound, and transparently and objectively described in the Toxicological Review. Considerations include the scientific support regarding the plausibility for the hypothesized MOA and the characterization of uncertainty regarding this MOA.

3. EPA has proposed a MOA for female mouse forestomach tumors involving metabolism, irritation and regenerative proliferation leading to tumor induction as key events best supported by the data. Please provide detailed comments on whether this analysis regarding the MOA for forestomach tumors is scientifically sound, and transparently and objectively described in the Toxicological Review. Considerations include the scientific support regarding the plausibility for the hypothesized MOA and the characterization of uncertainty regarding this MOA.

4. EPA has not proposed a MOA for the female rat pheochromocytomas of the adrenal medulla. NTP rated the female rat pheochromocytomas as providing equivocal evidence of carcinogenic activity and the pathology report expressed concern as to whether the observed tumors met the criteria used to diagnose pheochromocytomas. For these reasons, this tumor was not given significant weight in the qualitative or quantitative assessment of EGBE cancer potential. Please provide detailed comments on whether this analysis regarding the female rat pheochromocytomas is scientifically sound, and transparently and objectively described in the Toxicological Review. Please comment on whether and the extent to which the female rat pheochromocytomas are adequate to support alternative analyses of qualitative and quantitative cancer risks to humans and discuss approaches to consider if such analyses are warranted.

5. Please comment on the choice of the nonlinear threshold approach for the quantitative assessment of the carcinogenic potential of EGBE. Please comment on whether this approach is scientifically sound, and transparently and objectively described. Please comment on whether the example calculations using linear low-dose extrapolation for cancer as discussed in section 5.4.1 represent useful characterizations of the potential quantitative uncertainty associated with exposure to EGBE. Please comment on whether the linear analysis should be presented as an alternative to the threshold approach considering the Agency conclusion that EGBE is *not likely to be carcinogenic to humans* at expected exposure concentrations.