Draft Charge to the Science Advisory Board for the
IRIS Toxicological Review of ethyl tertiary butyl ether (ETBE)

August 2016

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of draft Toxicological Review of ethyl tertiary butyl ether (ETBE) developed in support of the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

IRIS is a human health assessment program that evaluates scientific information on effects that may result from exposure to specific chemical substances in the environment. Through IRIS, EPA provides high quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health. IRIS assessments contain information for chemicals that can be used to support hazard identification and dose-response assessment, two of the four steps in the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for health effects (including cancer and effects other than cancer) resulting from chronic exposure. IRIS toxicity values may be combined with exposure information to characterize public health risks of chemicals; this risk characterization information can then be used to support risk management decisions.

There is no existing IRIS assessment for ETBE. IRIS is developing this assessment in tandem with that of *tert*-butyl alcohol (*tert*-butanol) because *tert*-butanol is a major metabolite of ETBE, so data from one compound may be informative as to the toxicity of the other compound. The draft Toxicological Review of ETBE is based on a comprehensive review of the available scientific literature on the noncancer and cancer health effects in humans and experimental animals exposed to ETBE. Additionally, appendices for chemical and physical properties, toxicokinetic information, and other supporting materials are provided as *Supplemental Information* (see Appendices A to C) to the draft Toxicological Review.

The draft assessment was developed according to guidelines and technical reports published by EPA (see *Preamble*), and contain both qualitative and quantitative characterizations of the human health hazards for ETBE, including a cancer descriptor of the chemical's human carcinogenic potential, noncancer toxicity values for chronic oral (reference dose, RfD) and inhalation (reference concentration, RfC) exposure, and cancer risk estimates for oral and inhalation.

Charge questions on the draft ETBE Toxicological Review

1. **Literature search/study selection and evaluation**. The section on *Literature Search Strategy | Study Selection and Evaluation* describes the process for identifying and selecting pertinent studies. Please comment on whether the literature search strategy, study selection considerations, and study evaluation considerations are appropriate and clearly described. Please identify additional peer-reviewed studies that the assessment should consider.

2. **Toxicokinetic modeling.** In Appendix B, the draft assessment describes a physiologically-based pharmacokinetic (PBPK) model for ETBE in rats that was adapted from published models for MTBE (Blancato et al., 2007) and *tert*-butanol (Leavens and Borghoff, 2009).

   2a. Does this PBPK model (Salazar et al., 2015) adequately represent the toxicokinetics? Are the model assumptions and parameters clearly presented and scientifically supported? Are the uncertainties in the model structure appropriately considered and discussed?

   2b. The rate of ETBE metabolism was selected as the dose metric for the dose-response assessment. Is the choice of dose metric appropriate? Does this PBPK model adequately estimate the internal dose of ETBE in rats?

3. **Hazard identification and dose-response assessment.** In Chapter 1, the draft assessment evaluates the available human, animal, and mechanistic studies to identify health outcomes that may result from exposure to ETBE. In Chapter 2, the draft assessment develops organ/system-specific reference values for the health outcomes identified in Chapter 1, then selects overall reference values for each route of exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance) to reach the following conclusions.

   [Note: As suggested by the Chemical Assessment Advisory Committee panel that reviewed the draft IRIS assessment of benzo[a]pyrene, the charge questions in this section are organized by health outcome, with a question on each hazard identification followed by questions on the corresponding organ/system-specific toxicity values. This suggestion, however, entails some redundancy, as some questions apply equally to multiple health outcomes.]

   3a. **Kidney toxicity.**

   i) **Kidney hazard** (Sections 1.2.1, 1.3.1). The draft assessment concludes that kidney effects are potential human hazards of ETBE exposure. Please comment on whether the available human, animal, and mechanistic studies support this conclusion, giving due consideration to the relationships between several observed endpoints and the alpha2u-globulin process and/or chronic progressive nephropathy.

   ii) **Kidney-specific oral toxicity values** (Section 2.1.1). The draft assessment selects four studies (Suzuki et al. (2012), Miyata et al. (2013), Gaoua et al. (2004b), and Fujii et al. (2010)) to quantify kidney effects. Is this selection of studies scientifically supported and clearly described?

iii) **Points of departure for kidney endpoints** (Section 2.1.2). Are the calculation of points of departure from endpoints reported in Suzuki et al. (2012), Miyata et al. (2013), Gaoua et al. (2004b), and Fujii et al. (2010) studies, including urothelial hyperplasia, scientifically supported and clearly described?

iv) **Uncertainty factors for kidney endpoints** (Section 2.1.3). Is the application of uncertainty factors to these points of departure is scientifically supported and clearly described?

v) **Kidney-specific oral reference dose** (Section 2.1.4). Is the organ/system-specific oral reference dose derived for kidney effects is scientifically supported and clearly characterized?

vi) **Kidney-specific inhalation toxicity values** (Sections 2.2.1 – 2.2.3). Are the points of departure from the Saito et al. (2013), Medinsky et al. (1999), and JPEC (2008b) studies, as well as application of uncertainty factors are scientifically supported and clearly described?

vii) **Kidney-specific inhalation reference concentration** (Section 2.2.4). Is the organ/system-specific inhalation reference concentration derived for kidney effects is scientifically supported and clearly characterized?

3b. **Liver effects**

i) **Liver hazard** (Section 1.2.2). The draft assessment concludes that there is suggestive evidence of liver effects associated with ETBE exposure. Please comment on whether the available human, animal, and mechanistic studies support this conclusion.

3c. **Reproductive effects**

i) **Reproductive hazard** (Section 1.2.3). The draft assessment states that, at this time, no conclusions are drawn in regard to reproductive system toxicity. Please comment on whether the available human, animal, and mechanistic studies support this conclusion.

3d. **Developmental effects**

i) **Developmental hazard** (Section 1.2.4). The draft assessment concludes that the developmental toxicity evidence is slight and uncertain, and the toxicological significance is unknown. Do the available human, animal, and mechanistic studies support this statement?

3e. **Other types of toxicity** (Section 1.2.6). The draft assessment concludes that, at this time, there is inadequate information to draw conclusions regarding other health hazards that may be associated with ETBE exposure. Do the available human, animal, and mechanistic studies support these statements?

3f. **Cancer**

i) **Cancer hazard** (Sections 1.2.1, 1.2.2, 1.2.5, 1.3.2). There are plausible scientific arguments for more than one hazard descriptor, as discussed in Section 1.3.2. The draft

assessment concludes that there is *suggestive evidence of carcinogenic potential* for ETBE. Please comment on whether the available human, animal, and mechanistic studies support this conclusion in accordance with the EPA Cancer Guidelines (2005).

ii) **Cancer modes of action** (Sections 1.2.2, 1.3.2). A mode of action for the nuclear hormone receptors (i.e. PPARα, PXR and/or CAR) was evaluated and the draft assessment concludes that there is inadequate evidence to determine the role these pathways play, if any, in ETBE-induced liver carcinogenesis. Acetaldehyde-mediated genotoxicity was also evaluated as a possible MOA, but while suggestive, the available data overall are insufficient to establish acetaldehyde-mediated mutagenicity as a MOA for ETBE-induced liver tumors. Overall, the draft assessment concludes that the data are inadequate to establish a nuclear hormone receptor- or acetaldehyde-mediated MOA for liver carcinogenesis, and in accordance with the EPA Cancer Guidelines (2005), the liver tumors induced by ETBE are relevant to human hazard identification. Do the available human, animal, and mechanistic studies support this conclusion?

iii) **Cancer oral toxicity values** (Section 2.3.1). As noted in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*:
"When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities."

The draft assessment uses a PBPK model to derive an oral toxicity value from the 2-year inhalation Saito et al. (2013) study. Does the draft assessment adequately explain the rationale for quantitative analysis? Is the selection of the Saito et al. (2013) study for this purpose scientifically supported and clearly described?

iv) **Cancer inhalation toxicity values** (Section 2.4.1). As noted in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*:
"When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities."

Does the draft assessment adequately explain the rationale for quantitative analysis? Is the selection of the Saito et al. (2013) study for this purpose scientifically supported?

v) **Points of departure for cancer** (Sections 2.3.2, 2.3.3, 2.4.2, 2.4.3). Because an MOA could not be established for liver carcinogenesis, the draft assessment uses linear extrapolation below the points of departure based upon liver tumors. Please discuss whether the calculation of points of departure and oral and inhalation slope factors is scientifically supported in accordance with the EPA Cancer Guidelines (2005), and clearly described.

4. **Dose-response analysis.** In Chapter 2, the draft assessment uses the available human, animal, and mechanistic studies to derive candidate values and organ/system-specific toxicity values for each hazard that is credibly associated with ETBE exposure in Chapter 1, then selects an

overall toxicity value for each route of exposure. The draft assessment uses EPA's guidance documents (http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance) in the following analyses.

4a. **Oral reference dose for effects other than cancer** (Sections 2.1.5, 2.1.6). The draft assessment derives an overall oral reference dose of $5x10^{-1}$ mg/kg-day based on kidney urothelial hyperplasia as described in Suzuki et al., 2012. Is this selection is scientifically supported and clearly described?

4b. **Inhalation reference concentration for effects other than cancer** (Sections 2.2.5, 2.26). The draft assessment proposes an overall reference concentration of $9x10^{0}$ mg/m^3 based on kidney urothelial hyperplasia as describe in Saito et al., 2013. Is this selection is scientifically supported and clearly described?

4c. **Oral slope factor for cancer** (Sections 2.3.3, 2.3.4). The draft assessment derives an oral slope factor of $9x10^{-4}$ per mg/kg-day based on the liver adenoma or carcinoma response in male rats, using a PBPK model to extrapolate the inhalation point of departure to an oral point of departure. Is this value scientifically supported and clearly described?

4d. **Inhalation unit risk for cancer** (Sections 2.4.3, 2.4.4). The draft assessment derives an inhalation unit risk of $8x10^{-5}$ per mg/m^3 based on liver adenomas and carcinoma in male rats. Is this value scientifically supported and clearly described?

5. **Executive summary**. Does the executive summary clearly and appropriately present the major conclusions of the assessment?