Charge to the Science Advisory Board for the
IRIS Toxicological Review of *tert*-butyl alcohol

September 2014

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of draft Toxicological Review of *tert*-butyl alcohol (*tert*-butanol) 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 chemical substances 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 chemical substances; this risk characterization information can then be used to support risk management decisions.

There is no existing IRIS assessment for *tert*-butanol. IRIS is developing this assessment in tandem with that of ethyl *tert*-butyl ether (ETBE) 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 *tert*-butanol 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 *tert*-butanol. 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 *tert*-butanol, 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 *tert*-butanol Toxicological Review

1. **Literature search/study selection**. Is the literature search strategy well documented? Please identify additional peer-reviewed studies that might have been missed.

2. **Physiologically-based pharmacokinetic (PBPK) modeling.** In Appendix B, the draft assessment describes the development of an EPA PBPK model for *tert*-butanol 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 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 concentration of *tert*-butanol in the blood was selected as the dose metric to derive the BMCL. Is the choice of dose metric appropriate? Does this PBPK model adequately estimate the internal dose of *tert*-butanol in rats?

3. **Hazard identification.** In section 1, the draft assessment evaluates the available human, animal, and mechanistic studies to identify the types of toxicity that can be credibly associated with *tert*-butanol exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/backgrd.html/) to reach the following conclusions.

   3a. **Kidney toxicity** (section 1.1.1, 1.2.1). The draft assessment concludes that kidney toxicity is a human hazard of *tert*-butanol exposure. Do the available human, animal, and mechanistic studies support this conclusion, giving due consideration to the mode of action analyses for alpha2u-globulin nephropathy and chronic progressive nephropathy?

   3b. **Thyroid toxicity** (sections 1.1.2, 1.2.1). The draft assessment concludes that thyroid toxicity is a potential human hazard of *tert*-butanol exposure. Do the available human, animal, and mechanistic studies support this conclusion?

   3c. **Developmental toxicity** (sections 1.1.3, 1.2.1). The draft assessment concludes that there is suggestive evidence of developmental toxicity as a potential human hazard of *tert*-butanol exposure. Do the available human, animal, and mechanistic studies support this conclusion?

   3d. **Other types of toxicity** (sections 1.1.3, 1.1.5, 1.2.1). The draft assessment concludes that the evidence does not support other types of noncancer toxicity as a potential human hazard of *tert*-butanol exposure. Are there other types of noncancer toxicity that can be credibly associated with *tert*-butanol exposure?

   3e. **Cancer** (sections 1.1.1, 1.1.2, 1.1.4, 1.2.2). The draft assessment concludes that there is "suggestive evidence of carcinogenic potential" for *tert*-butanol by all routes of exposure. Do the available human, animal, and mechanistic studies support this conclusion, giving due consideration to the mode of action analyses for alpha2u-globulin nephropathy, chronic progressive nephropathy, and thyroid follicular cell tumors?

4. **Dose-response analysis.** In section 2, the draft assessment uses the available human, animal, and mechanistic studies to derive candidate toxicity values for each hazard that is credibly associated with *tert*-butanol exposure in section 1, then proposes an overall toxicity value for

each route of exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/backgrd.html/) in the following analyses.

4a. **Oral reference dose for effects other than cancer** (section 2.1). The draft assessment proposes an overall reference dose of $1x10^{-1}$ mg/kg-d based on kidney transitional epithelial hyperplasia. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, and applying uncertainty factors?

4b. **Inhalation reference concentration for effects other than cancer** (section 2.2). The draft assessment proposes an overall reference concentration of $9x10^{-1}$ mg/m^3 based on kidney transitional epithelial hyperplasia, using a PBPK model to extrapolate the oral point of departure to an inhalation point of departure. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, route-to-route extrapolation, and applying uncertainty factors?

4c. **Oral slope factor for cancer** (section 2.3). The draft assessment proposes an oral slope factor of $1x10^{-2}$ per mg/kg-d based on kidney tumors in rats. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis and calculating points of departure?

4d. **Inhalation unit risk for cancer** (section 2.4). The draft assessment proposes an inhalation unit risk of $1x10^{-3}$ per mg/m^3 based on kidney tumors in rats, using a PBPK model to extrapolate the oral point of departure to an inhalation point of departure. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, and route-to-route extrapolation?

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

Charge question on the public comments

6. In [DATE TBD], EPA asked for public comments on an earlier draft of this assessment. Appendix D summarizes the public comments and this assessment's responses to them. Please comment on EPA's responses to the scientific issues raised in the public comments.