Draft Charge to the Science Advisory Board for the IRIS Toxicological Review of *tert*-Butyl Alcohol

April 2016

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of the 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 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 *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 toxicokinetic information, dose-response modeling, 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 contains 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 a cancer risk estimate for oral exposure.

Charge questions on the draft Toxicological Review of *tert*-butanol

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 *tert*-butanol in rats that EPA modified (Salazar et al., 2015) 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 daily average concentration of *tert*-butanol in the blood 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 *tert*-butanol 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 *tert*-butanol. 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 effects.**

   i) **Kidney hazard** (Sections 1.2.1, 1.3.1). The draft assessment concludes that kidney effects are potential human hazards of *tert*-butanol 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. Please comment on whether this selection is scientifically supported and clearly described.
   ii) **Kidney-specific oral toxicity values** (Section 2.1.1). Please comment on whether the selection of the NTP (1995) study that describes kidney effects is scientifically supported and clearly described.
   iii) **Points of departure for kidney endpoints** (Section 2.1.2). Please comment on whether the calculation of points of departure from endpoints reported in NTP (1995)

study, including transitional epithelial hyperplasia, is scientifically supported and clearly described.

iv) **Uncertainty factors for kidney endpoints** (Section 2.1.3). Please comment on whether 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). Please comment on whether 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). The draft assessment uses a PBPK model to derive inhalation toxicity values from the 2-year oral NTP (1995) study. Please comment on whether the selection of the 2-year oral NTP (1995) study (with application of toxicokinetic modeling to extrapolate from oral to inhalation exposures) over the 13-week inhalation NTP (1997) study is scientifically supported and clearly described. Please comment as to whether calculation of points of departure from the NTP (1995) study, as well as application of uncertainty factors to both inhalation and oral exposure-derived points of departure, are scientifically supported and clearly described.

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

3b. **Developmental effects**

i) **Developmental hazard** (Section 1.2.3). The draft assessment concludes that there is suggestive evidence of developmental effects associated with tert-butanol exposure. Please comment on whether the available human, animal, and mechanistic studies support this conclusion.

ii) **Neurodevelopmental hazard** (Section 1.2.4). The draft assessment states that, at this time, there is inadequate information to draw conclusions regarding neurodevelopmental toxicity. Please comment on whether the available human, animal, and mechanistic studies support this conclusion.

3c. **Reproductive effects**

i) **Reproductive hazard** (Section 1.2.5). 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. **Other toxicological effects** (Section 1.2.6). The draft assessment states that, at this time, there is inadequate information to draw conclusions regarding other health hazards that may be associated with *tert*-butanol exposure. Please comment on whether the available human, animal, and mechanistic studies support these conclusions.

3e. **Cancer.**

i) **Cancer hazard** (Sections 1.2.1, 1.2.2, 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 *tert*-butanol. Please comment on whether the available human, animal, and

mechanistic studies support this conclusion in accordance with the relevant U.S. EPA Guidelines (2005).

ii) **Cancer modes of action:**

(1) Kidney (Sections 1.2.1, 1.3.2). A mode of action for the alpha2u-globulin process was evaluated (U.S. EPA, 1991); the draft assessment concludes that *tert*-butanol weakly induces this process, and that this process is not solely responsible for the renal tubule nephropathy and carcinogenicity observed in male rats. A chronic progressive nephropathy mode of action was also evaluated; the draft assessment concludes that although chronic progressive nephropathy was indicated in the induction of renal tubule toxicity, it does not induce renal tubule tumors in male rats. Overall, the draft assessment concludes that other, unknown processes contribute to renal tubule nephrotoxicity and carcinogenicity, and that the kidney tumors in male rats are relevant to human cancer hazard identification. Please comment on whether the available human, animal, and mechanistic studies support this conclusion in accordance with the relevant U.S. EPA Guidelines (1991).

(2) Thyroid (Sections 1.2.2, 1.3.2). An anti-thyroid mode of action was evaluated (U.S. EPA, 1998); the draft assessment concludes that the evidence is inadequate to determine if an antithyroid MOA is operating, and that the thyroid tumors in male and female mice are relevant to human cancer hazard identification. Please comment on whether the available human, animal, and mechanistic studies support this conclusion in accordance with the relevant U.S. EPA Guidelines (1998).

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."

Please comment on whether the draft assessment adequately explains the rationale for quantitative analysis, and whether the selection of the NTP (1995) study for this purpose is scientifically supported and clearly described.

iv) **Points of departure for cancer** (Sections 2.3.2, 2.3.3). Because the relative contribution of α2u-globulin nephropathy and other processes to kidney tumorigenesis in male rats could not be determined, the draft assessment concludes that the rat kidney tumors cannot be used in dose-response analysis (U.S. EPA. 1991). Because evidence was inadequate to determine if an antithyroid MOA is operating, the draft assessment uses linear extrapolation below the points of departure bases upon thyroid tumors (U.S. EPA, 1998). Please comment on whether the calculation of points of departure and oral slope factors is scientifically supported in accordance with the relevant U.S. EPA Guidelines (1991, 1998, 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 *tert*-butanol exposure in Chapter 1, then selects an overall toxicity value 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) 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 1×10^{-1} mg/kg-day based on kidney transitional epithelial hyperplasia as described in NTP (1995). Please comment on whether this selection is scientifically supported and clearly described.

4b. **Inhalation reference concentration for effects other than cancer** (Sections 2.2.5–2.2.6). The draft assessment derives an overall inhalation reference concentration of 9×10^{-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. Please comment on whether 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 5×10^{-4} per mg/kg-day based on the thyroid follicular cell adenoma or carcinoma response in male and female mice. Is this value scientifically supported and clearly described?

4d. **Inhalation unit risk for cancer** (Section 2.4). No inhalation unit risk was derived in the draft assessment. There are no chronic inhalation studies for *tert*-butanol. No mouse PBPK model is available to extrapolate the oral thyroid tumor results to the inhalation route. If the available data might support an inhalation unit risk, please describe how one might be derived.

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