

Revised 7/26/17 by the CAAC-ETBE/tBA committee per discussion during the July 11, 2017, teleconference. Changes are presented as underlined text.

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

June 2017

Introduction

EPA thanks the expert scientists on the augmented SAB Chemical Assessment Advisory Committee for reviewing this draft assessment.

This draft assessment reviews publicly available studies on *tert*-butanol to identify adverse health outcomes and to characterize exposure–response relationships. Peer review is essential to the quality and integrity of IRIS assessments, which provide scientific information that supports EPA’s actions to protect public health. The draft assessment was reviewed by scientists across EPA and other federal agencies. EPA also solicited public comment and convened a public science meeting to discuss major science issues. Experts identified by the National Academy of Sciences participated in the public discussions. Responses to major public comments appear as supplemental material to the draft assessment.

EPA is seeking SAB advice on the clarity and scientific underpinnings of the overall assessment. The peer review should consider whether the conclusions presented in the draft assessment are clearly presented and scientifically supported. Below, a set of charge questions for each major analysis are presented. The SAB is expected to consider questions and issues raised during public comment as part of its deliberations. The advice will be most useful when prioritized to indicate its relative importance during revision:

- *Tier 1: Recommended Revisions* – Key recommendations that are necessary in order to improve the critical scientific concepts, issues and/or narrative within the assessment.
- *Tier 2: Suggestions* – Recommendations that are encouraged for EPA to adopt in order to strengthen the scientific concepts, issues and/or narrative within the assessment, but other factors (e.g., Agency need) should be considered by EPA before undertaking these revisions.
- *Tier 3: Future Considerations* – Useful and informative scientific exploration that may inform future evaluations of key science issues and/or the development of future assessments. These recommendations are likely outside the immediate scope and/or needs of the current assessment under review.

1. Literature Search Strategy/ Study Selection and Evaluation- Systematic Review Methods

Please comment on the strategies for literature searches, criteria for study inclusion or exclusion, and evaluations of study methods and quality discussed in the Literature Search Strategy/ Study Selection and Evaluation section. Were the strategies clearly described and objectively applied?

Hazard Identification and Dose-Response Analysis

Chapter 1 (Hazard Identification) and the supplemental materials summarize the chemical properties, toxicokinetics, and health effects associated exposure to *tert*-butanol. Chapter 2 (Dose Response Analysis) uses this information to derive an oral reference dose and inhalation reference concentration for noncancer outcomes, in addition to an oral slope factor for cancer.

2. Chemical Properties and Toxicokinetics

2a. Chemical properties. Is the information on chemical properties accurate?

2b. Toxicokinetic modeling. Section B.1.5 of Appendix B in the Supplemental Information describes the application and modification of a physiologically-based toxicokinetic model of *tert*-butanol in rats (Borghoff et al., 2016). Is use of the model appropriate and clearly described, including assumptions and uncertainties? Are there additional peer-reviewed studies that should be considered for modeling?

2c. Choice of dose metric. Is the average concentration of *tert*-butanol in blood an appropriate choice for the dose metric?

Hazard Identification and Dose-Response Assessment

Comment on EPA's assessment of the toxicological studies and dose-response assessment, including whether there are additional peer-reviewed studies that should be considered.

3. Noncancer

3a. Noncancer kidney toxicity (Sections 1.2.1, 1.3.1). The draft assessment identifies kidney effects as a potential human hazard of *tert*-butanol. EPA evaluated the evidence, including the role of α 2u-globulin and chronic progressive nephropathy, in accordance with EPA guidance (U.S. EPA, 1991). Please comment on whether this conclusion is scientifically supported and clearly described.

3b. Noncancer toxicity at other sites. (Sections 1.2.3-6, and 1.3.1). The draft assessment finds inadequate information to assess developmental, neurodevelopmental, and reproductive toxicity. Please comment on whether these conclusions are scientifically supported and clearly described. If there are publicly available studies to associate other health outcomes with *tert*-butanol exposure, please identify them and outline the rationale for including them in the assessment.

3c. Oral reference dose for noncancer kidney outcomes. Section 2.1 presents an oral reference dose of 4×10^{-1} mg/kg-day, based on increases in severity of nephropathy in female

rats via drinking water (NTP, 1995). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative data set or approach would be more appropriate, please outline how such data might be used or how the approach might be developed.

3d. Inhalation reference concentration for noncancer outcomes. Section 2.2 presents an inhalation reference concentration of 5×10^0 mg/m³, based on increases in severity of nephropathy in female rats via drinking water (NTP, 1995), converted for inhalation exposure using a toxicokinetic model (Borghoff et al., 2016). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative data set or approach would be more appropriate, please outline how such data might be used or the approach might be developed.

4. Cancer

4a. Cancer modes-of-action.

(i) Cancer modes-of-action in the kidney. As described in section 1.2.1, kidney tumors were observed in male rats following *tert*-butanol exposure, and a mode-of-action involving α_{2u} -globulin and/or chronic progressive nephropathy was evaluated. The analysis, conducted in accordance with EPA's guidance on renal toxicity and neoplasia in the male rat (U.S. EPA, 1991), considered the kidney tumors in male rats to be relevant to human hazard identification. Please comment on whether this conclusion is scientifically supported.

(ii) Cancer modes-of-action in the thyroid. As described in section 1.2.2, thyroid tumors were observed in male and female mice following *tert*-butanol exposure, and an anti-thyroid mode-of-action was evaluated. The analysis, conducted in accordance with EPA's guidance on thyroid follicular cell tumors in rodents (U.S. EPA, 1998), found the information inadequate to determine whether an anti-thyroid mode-of-action was operating and considered the thyroid follicular cell tumors in male and female mice to be relevant to humans. Please comment on whether this conclusion is scientifically supported.

4b. Cancer characterization. As described in sections 1.2.1, 1.2.2, and 1.3.2, and in accordance with EPA's cancer guidelines (U.S. EPA, 2005), the draft assessment concludes that there is *suggestive evidence of carcinogenic potential* for *tert*-butanol, based on thyroid follicular cell tumors in male and female B6C3F₁ mice via drinking water and on renal tubule tumors in male F344 rats via drinking water. ~~Please comment on whether this cancer descriptor is scientifically supported. If another cancer descriptor should be selected, please outline how it might be supported. Please comment on whether the "suggestive evidence" cancer descriptor is scientifically supported for all routes of exposure. If another cancer descriptor should be selected, please outline how it might be supported.~~

4c. Cancer toxicity values. Section 3 of EPA's cancer guidelines (2005) states:

“When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as 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. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence.”

~~Please comment on whether Section 2.3 of the draft assessment adequately explains the rationale for quantitative analysis, and whether the NTP (1995) study is suitable for this purpose.~~ Please comment on whether Sections 2.3 of the draft assessment adequately explains the rationale for including a quantitative analysis given the “suggestive evidence” descriptor. Also comment whether the NTP (1995) study is a suitable basis for this quantitative analysis.

4d. Oral slope factor for cancer. Section 2.3 presents an oral slope factor of 5×10^{-4} per mg/kg-day, based on thyroid tumors in male or female mice via drinking water (NTP, 1995). Please comment on whether this value is scientifically supported and its derivation clearly described. If an alternative approach would be more appropriate, please outline how it might be developed.

4e. Inhalation unit risk for cancer. Section 2.4 presents no inhalation unit risk. The lack of a toxicokinetic model for mice precluded the use of the oral thyroid tumor data, and the inability to determine the relative contribution of $\alpha_2\text{-u}$ -globulin nephropathy and other processes precluded the use of the oral renal tumor data from male rats. If an alternative approach would yield an inhalation unit risk estimate, please outline how it might be developed.

5. Susceptible Populations and Lifestages

As described in Section 1.3.3, the draft assessment found inadequate information to identify susceptible populations or lifestages, due to a lack of chemical-specific data. Please comment on whether this conclusion is scientifically supported and clearly described. If there are publicly available studies to identify other susceptible populations or lifestages, please identify them and outline their impact on the conclusions.

6. Question on the Executive Summary

The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions for a broad range of audiences. Please comment on whether the executive summary clearly and appropriately presents the major conclusions of the draft assessment.