EPA's Response to Select Interagency Comments on the Interagency Science Consultation Draft of the IRIS Toxicological Review of *tert*-Butyl Alcohol

May 2016

Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where the Executive Office of the President and other federal agencies can comment on draft assessments. Comments on the Interagency Science Consultation draft of the IRIS Toxicological Review of *tert*-Butyl Alcohol (*tert*-butanol) (Step 3) were provided by the National Toxicology Program (NTP), and jointly by the Office of Management and Budget (OMB) and the Office of Science and Technology Policy (OSTP). The following are EPA's responses to select interagency comments. All interagency comments were taken into consideration in revising the draft assessment prior to release for public comment (Step 4a).

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

Select Interagency Science Consultation Comments and Responses:

Topic #1: Confusion regarding α_{2u}-globulin nephropathy - *OMB commented that there was contradictory language in the assessment regarding the conclusions related to α_{2u}-globulin nephropathy and kidney effects.*

EPA Response: EPA has revised and added text in the document to improve the clarity of the α_{2u}-globulin mode-of-action (MOA) analysis, discussion, and conclusions presented in Sections 1.2.1, 1.3.1, 1.3.2, 2.2.8, 2.3.1, 2.3.4, and 2.4, as well as the Executive Summary. Noncancer kidney endpoints that are considered part of the α_{2u}-globulin nephropathy pathological sequence are specific to the male rat, and are not relevant for human health assessment. Thus, these endpoints are not considered in the hazard identification and dose-response assessment for *tert*-butanol. With respect to carcinogenicity, EPA concluded that α_{2u}-globulin nephropathy was likely responsible for some but not all of the kidney tumors. Thus, these tumors were considered in the characterization of the carcinogenic potential of *tert*-butanol. Because α_{2u}-globulin nephropathy was not the sole MOA for kidney tumors, and the relative contribution of this process to tumor development could not be ascertained, the kidney tumors were not considered in the dose-response assessment for cancer risk.

Topic #2: PBPK modeling – *NTP commented that it is not clear why reversible protein binding in the blood was added in the PBPK model to account for the fact that 60% of the radiolabeled tert-butanol in whole blood is in plasma.*

EPA Response: EPA has revised the document to better explain how the PBPK model was modified. As described in Appendix B.2.2. of the Supplemental Information, the model includes reversible binding of *tert*-butanol in the blood to improve the fit of the model to the *tert*-butanol blood concentrations measured after i.v. dosing data of Poet et al. (1997). The impact of this modification is that the bound *tert*-butanol is not considered free *tert*-butanol in blood.

Topic #3: Evidence that *tert*-butanol is a developmental toxicant is weak – *NTP commented that the evidence for tert-butanol being a developmental toxicant is weak and if it occurs at all is at extraordinarily high doses and likely to be of limited human relevance.*

EPA Response: Exposure to *tert*-butanol during gestation resulted in increased fetal loss, decreased fetal body weight, and increases in skeletal variations in exposed offspring. As noted by NTP, these effects were observed at relatively high doses (e.g., 1000 mg/kg-day), and while skeletal variations were noted, no malformations were reported. At these same doses, the mothers also had body weight losses or gains (or both), decreased food consumption, and clinical signs of intoxication. Therefore, determining whether *tert*-butanol exposure results in specific developmental toxicity or whether the fetal effects are due to maternal toxicity is difficult. The observed maternal effects are minimal, however, and thus, the developmental effects observed in the fetuses are not discounted as being secondary to maternal toxicity (U.S. EPA, 1991). Overall, the evidence is considered suggestive of developmental toxicity. Although EPA considered there to be some evidence for developmental toxicity, these effects were observed at high doses which also affected the mothers, and there was a lack of consistency across some endpoints. In addition, no adverse effects were reported in one- and two-generation developmental studies on the parent compound of *tert*-butanol, ethyl tertiary butyl ether (ETBE) (Gaoua, 2004a, b). Due to the limited evidence for developmental toxicity, EPA did not carry the developmental endpoints forward for dose-response analysis.

References

Gaoua, W. (2004a). Ethyl tertiary butyl ether (ETBE): prenatal developmental toxicity study by the oral route (gavage) in rats. (CIT Study No. 24860 RSR). unpublished study for Totalfinaelf on behalf of the ETBE Producers' Consortium.

Gaoua, W. (2004b). Ethyl tertiary butyl ether (ETBE): Two-generation study (reproduction and fertility effects) by the oral route (gavage) in rats. (CIT Study No. 24859 RSR). unpublished study for Totalfinaelf on behalf of the ETBE Producers' Consortium.

Poet, TS; Valentine, JL; Borghoff, SJ. (1997). Pharmacokinetics of tertiary butyl alcohol in male and female Fischer 344 rats. Toxicol Lett 92: 179-186.

U.S. EPA (U.S. Environmental Protection Agency). (1991). Guidelines for developmental toxicity risk assessment. (EPA/600/FR-91/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162.