EPA's Response to Select Interagency Comments on the Interagency Science Consultation Draft of the IRIS Toxicological Review of Ethyl Tertiary Butyl Ether

August 2016

Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where other federal agencies and the Executive Office of the President can comment on draft assessments. Comments on the Interagency Science Consultation (step 3) draft of the IRIS Toxicological Review of ethyl tertiary butyl ether (ETBE) were provided by the National Toxicology Program (NTP) and the Office of Management and Budget (OMB)/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: Compare dose response relationship for both ETBE and tert-butanol. – *NTP commented that it would be interesting to compare the kidney toxicity data for both ETBE and tert-butanol using tert-butanol blood concentrations as the dose metric.*

> **EPA Response**: EPA has performed a separate analysis comparing kidney effects induced by ETBE and *tert*-butanol on the basis of internal dose. The results demonstrated that noncancer kidney effects, including kidney weight changes, urothelial hyperplasia, and chronic progressive nephropathy (CPN), yielded consistent dose-response relationships using *tert*-butanol blood concentration as the dose metric. Kidney tumors were not consistent using any dose metric. These results appear in the Supplemental Information and have also been published in Salazar et al. (2015).
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> **Reference:**
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> Salazar, KD; Brinkerhoff, CJ; Lee, JS; Chiu, WA. (2015). Development and application of a rat PBPK model to elucidate kidney and liver effects induced by ETBE and tert-butanol. Toxicol Appl Pharmacol 288: 439-452. http://dx.doi.org/10.1016/j.taap.2015.08.015.

Topic #2: OMB asked to add a follow-up to the charge question regarding cancer. - *"Has EPA presented sufficient justification for deriving an oral slope factor and an inhalation unit risk when the cancer descriptor of "suggestive evidence" was concluded?"*

> **EPA Response:** The following charge question was added for the oral toxicity value with a similar charge question added for the inhalation toxicity value:

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. Please comment on whether the draft assessment adequately explains the rationale for quantitative analysis, and whether the selection of the Saito et al. (2013) study for this purpose is scientifically supported and clearly described.