EPA's Response to Interagency Comments on the Final Interagency Science Discussion Draft of the IRIS Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE)

July 2021

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 Final Interagency Science Discussion draft of the IRIS Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE) were provided by the National Institute for Occupational Safety and Health (NIOSH) and the Office of Management and Budget (OMB). The following are EPA's responses to interagency comments. All interagency comments were taken into consideration in revising the draft assessment prior to posting on the IRIS database.

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

Interagency Science Discussion Comments and Responses:

Clarification regarding CPN human relevance- OMB commented that EPA may want clarify the language used to characterize the conclusions of NIEHS in their pathology consult to avoid the misperception that CPN itself is directly relevant to humans.

EPA Response: EPA clarified this text in Section ES.7 to more closely cite NIEHS: Given the fact that there is no definitive pathogenesis for CPN, it cannot be fully ruled out that chemicals which exacerbate CPN in rats may have the potential to exacerbate other disease processes in the human kidney (NIEHS, 2019).

Clarification regarding differences between ETBE and TBA cancer findings- OMB requested clarification of the discussion regarding differences in the database between ETBE and its metabolite TBA, specifically that while both appear to induce histological lesions in the alpha 2u-globulin pathway, ETBE did not result in renal tubule tumors whereas TBA did.

EPA Response*:* This text has been clarified in Section 1.2.1, *Mode-of-Action Analysis—Kidney Effects* to acknowledge remaining uncertainty regarding toxicokinetic and/or toxicodynamic differences across the two chemicals (see Section 1.2.1).

Expanding the RfC justification for selecting a POD from a chronic study over a lower POD from a subchronic study- NIOSH commented that additional text should be added to clarify in the

RfC section, as was done in the RfD section, the selection of a chronic kidney POD over lower subchronic PODs.

EPA Response: Text to clarify these points was added to Section 2.2.4.

Generally, chronic exposures are preferred over subchronic exposures to minimize uncertainty and extrapolation to a chronic exposure duration for deriving a reference value. In addition, the male kidney effects were not selecting due to potential confounding from alpha 2 u processes.

Suggestion of further PBPK modeling- NIOSH commented that to support whether ETBE induces liver tumors through acetaldehyde- mediated genotoxicity, a PBPK model, similar to that studied for *tert*-butanol and ETBE (Salazar et al., 2015), could be developed based on internal dose estimation.

EPA Response: Further development of the PBPK model to investigate a MOA based on acetaldehyde induced liver tumorigenesis could add increased plausibility to the MOA of acetaldehyde induced tumors (and potentially explain route specific differences in ETBE toxicity), but likely would not change any of the assessments conclusions (e.g. the cancer weight of evidence descriptor) and would not change any derived values. We note that developing a new PBPK model is considered a high level of effort endeavor. In consideration of the stage of this assessment (Step 6, post external peer review) new models and analyses, especially those that entail a high level of effort, are typically not considered unless strongly recommended by the external peer review committee.

Clarifying text relating to endpoints without statistical significance- OMB commented that if an effect is not found to be statistically significantly different, then it should not be considered different. This comment was regarding text discussing a non-statistically significant increase in hepatic basophilic lesions in male rats treated with ETBE by the oral route.

EPA Response: Statistical significance testing is an important tool for supporting a decision that there is a demonstrable effect, especially when biological significance of an outcome is uncertain or unclear. However, lack of statistical significance is not automatically interpreted as evidence of no effect. Both the biological and the statistical significance of effects are considered, and precedence is given to biological significance.

To clarify the statement about the non-statistically significant increased incidence of basophilic foci, incidence data (14/50, 18/50, 20/50, 22/50) was added for transparency in Section 1.2.2.