National Institute for Occupational Safety and Health (NIOSH)
Comments on the Interagency Science Discussion Draft
IRIS Assessment of Ethyl Tert-Butyl Ether July 2020
(Date Received August 25, 2020)

[Comments received via email. Substantiative comments summarized in EPA's Response to Selected Interagency Comments on the EPA IRIS Website]

Comments from the National Institute for Occupational Safety and Health (NIOSH) on the Environmental Protection Agency (EPA) IRIS Toxicological Review of Ethyl Tertiary Butyl Ether dated August 2020, EPA/635/R-20/106a, Final Agency/Interagency Draft (190 pages)

August 25, 2020

General Comments:

The selection of kidney weight increase from chronic exposure in female rats as a critical noncancer effect is well-reasoned given the relative confidence levels in the various toxicity datasets and the constellation of kidney-related effect levels reported in the data. These reasonings are well-documented in the text. The reference concentration (RfC) derived based on kidney weight effects in the chronic inhalation study in rats is similarly well-supported by the data. NIOSH notes that while EPA determined the level of confidence in the evidence for the critical effect to be "medium," the fact that multiple adverse kidney effects (kidney weights change, increased chronic progressive nephropathy (CPN) severity) converge on a similar point of departure adds support to the NOAEL as a critical point of departure despite not being a quantitative estimate.

EPA's decision to derive an IUR value makes best use of a limited data base, despite substantial gaps in the data. NIOSH appreciates EPA's clear articulation of their decisions and the detailed descriptions of the factors and methods involved. NIOSH notes that the lack of knowledge of the cancer mode of action (MOA) and the countervailing data from other cancer bioassays appear to be key limitations in evaluating whether liver tumors in male F344 rats are relevant to human risks. This is described briefly in Table 2-8; however, NIOSH suggests that additional clarity could be achieved by expanding the explanation in the text that knowledge of the MOA and/or more toxicity data from appropriate bioassays would likely strengthen the accuracy of the assessment.

Specific comments:

Page 1-6 lines 11-18: EPA notes the following:

> "CPN is an age-associated disease characterized by cell proliferation and chronic inflammation that results in increased kidney weight (Melnick et al., 2012; Travlos et al., 2011), thus animals severely affected by CPN, including those that died due to CPN, would be expected to have

enlarged kidneys. Although mortality in female rats in the 2-year inhalation study was also significantly increased, the study authors attributed these deaths to pituitary tumors, which would not be expected to bias measurement of kidney weight {JPEC, 2010, 1517421}. Mortality of male and female rats in the 2-year drinking water studies was not significantly different from controls {JPEC, 2010, 1517477}."

It is widely agreed that CPN is a sign of renal toxicity. However, two things could be clarified here. 1) Mortality in female rats is mentioned, but not in male rats. Were male rats significantly different from the control group or the female rats? This point is important given that across the animal studies evaluated for toxicity of ETBE or its active metabolite, *tert*-butanol, sex-specific severity in CPN has been identified. 2) Were the doses for 2-yr inhalation and 2-yr drinking water studies comparable? If yes, then route of exposure may play a key role in ETBE-induced toxic effects especially for cancer endpoints.

Page 1-6, Lines 25-27: "Increases in CPN graded as marked or severe were dose-related when compared on an internal dose basis across routes of exposure in male and female rats (Salazar et al., 2015)," which suggests an MOA for non-cancer endpoints. However, for cancer endpoints an additional metabolite such as acetaldehyde might be considered, other than internal dose.

Page 1-58, Lines 13-16: "Evidence suggests that metabolism of ETBE to acetaldehyde could contribute to ETBE-induced liver carcinogenesis. For instance, enhancement of ETBE-induced liver toxicity and genotoxicity has been reported in *Aldh2*-deficient mice, which have an impaired ability to metabolize acetaldehyde (Weng et al., 2013; Weng et al., 2012)." It is possible that carcinogenesis from ETBE is mediated through its metabolite *tert*-butanol, which has sufficient evidence to be considered genotoxic, or acetaldehyde, a known genotoxin and carcinogen. However, acetaldehyde has not been associated with liver tumors. 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.

Page 2-18, line 5 "Kidney Toxicity": EPA selects data from 2-yr studies to derive a risk value. The data presented in this section show that 13-week studies not only generated lower candidate RfC values, but also reported lower points of departure as well (up to 10-fold lower than the female kidney weight NOAEL from the Saito et al. study chosen for the RfC). The text implies that these may have been excluded for the same reasoning as their analogous entries in the oral toxicity RfD assessment (i.e., higher confidence in chronic studies and questionable relevance of male rat kidney endpoints), but this is not clear. Please articulate the reasoning, or clearly state that it is identical to the reasoning applied to the analogous data in the oral assessment.

Page 2-21, lines 13 & 14: It would help readability to clarify the meaning of "excessive toxicity" and why it did not apply in this case. This specific term is not widely used in this way and could be confusing to the reader.

Editorial comments:

Page xv, line 72: Change "facilitates" to facilitate.

Page xvii, line 12: Change to “life stages” instead of lifestages.