November 20, 2014
Interagency Review (Step 3) of EPA IRIS Toxicological Review of ETBE

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of ethyl tert-butyl ether (ETBE). We have comments on both the Preamble and the dose-response assessment.

Preamble Comments

There are statements in the Preamble that amount to policy positions or decisions rather than scientific ones. Several of these are noted here. The focus of the Preamble should be to describe the IRIS process as a scientific one. Please note that these comments are the same as those provided on the RDX draft toxicological review.

- p. xvi, lines 47-56: "**Step 5. Revision of draft Toxicological Review and development of draft IRIS summary**. The draft assessment is revised to reflect the peer review comments, public comments, and newly published studies that are critical to the conclusions of the assessment. The disposition of peer review comments and public comments becomes part of the public record."
    - Comment: Should there be text to explain that if necessary, the document may undergo a focused 2nd round peer review by the peer review panel? Is there a policy yet?
- p. xvi, line 60. Need period after the bold header sentence that begins with "Step 6."
- p. xvii, lines 65-66: "…some population-based surveys (for example, NHANES) provide the strongest epidemiological information…"
    - Comment: Population-based surveys, aka cross-sectional studies, should not be considered in the same category of clinical studies (which EPA has not mentioned), cohort studies, and case-control studies. Surveys have inherent methodological weaknesses that are well documented in epidemiological methodology texts, often to the extent that they are primarily considered hypothesis generating. The recommended remedy here is to split the first sentence, then add special reference to NHANES as a quality example of a survey design. "Cohort and case-control studies provide the strongest epidemiological evidence, especially if they collect information about individual exposures and effects. Population-based surveys, if conducted rigorously such as the NHANES survey, can also provide supportive information."
- p. xvii, lines 71-79: "Ecological studies (geographic correlation studies) relate exposures and effects by geographic area. They can provide strong evidence if there are large exposure contrasts between geographic areas, relatively little exposure variation within study areas, and population migration is limited. "
    - Comment: Aren't these types of studies typically considered to be the weakest study designs for establishing chemical/hazard relationships (i.e. associations or causality)? These are hypothesis generating studies, and not of the rigor for

demonstrating causality. Deleting the term “strong” would be a minimal necessary change to reflect this well-acknowledged limitation of ecological designs.

- p. xviii, lines 1-7: “Case reports of high or accidental exposure lack definition of the population at risk and the expected number of cases. They can provide information about a rare effect or about the relevance of analogous results in animals.”
    - Comment: There should be a caveat that case reports are (again) hypothesis generating types of studies (for potential hazard ID), and are inadequate for establishing causality.
- p. xviii, lines 46-51: “For developmental toxicity and reproductive toxicity, irreversible effects may result from a brief exposure during a critical period of development. Accordingly, specialized study designs are used for these effects (U.S. EPA, 2006b, 1998, 1996, 1991b).”
    - Comment: How will EPA treat the expansive literature exploring developmental tox endpoints that do not use the "specialized study designs" and instead are more "hypothesis generating" studies or academic laboratory studies? Many of these studies have been frequently cited in past tox reviews, but do not use the GLP study designs for regulatory purposes.
- p. xix, lines 65-76: “In some situations, examination of historical control data from the same laboratory within a few years of the study may improve the analysis. For an uncommon effect that is not statistically significant compared with concurrent controls, historical controls may show that the effect is unlikely to be due to chance. For a response that appears significant against a concurrent control response that is unusual, historical controls may offer a different interpretation (U.S. EPA, 60 2005a, §2.2.2.1.3).”
    - Comment: Is there any guidance on using historical control data in the manner suggested in this paragraph? Historical control data are typically used to measure "genetic drift" of the species being used in the laboratory, to ensure that laboratory practices are faithfully maintained according to adopted GLP or other guidances. Only concurrent control data provide an appropriate comparison to the treatment groups. This proposed practice – implied here as an agreed EPA policy -- would benefit from a more robust scientific discussion. Alternatively, deleting this section would have no detrimental effect on the preamble, and leave the issue to a case-by-case evaluation, which is where evaluation of historical controls ought be vis a vis individual study results.
- p. xix-xx, lines 85; 1-6: “Effects that occur at doses associated with mild maternal toxicity are not assumed to result only from maternal toxicity. Moreover, maternal effects may be reversible, while effects on the offspring may be permanent (U.S. EPA, 1998, §3.1.2.4.5.4; 1991, §3.1.1.4),.”
    - Comment: misplaced comma at the end of the sentence. There should also be a caveat explaining that exposures that result in frank maternal toxicity may not be relevant in producing the developmental toxicity of interest, i.e., the flip side of this statement.
- p. xx, lines 62-66: “The finding of a large relative risk with narrow confidence intervals strongly suggests that an association is not due to chance, bias, or other factors.”

- Comment: Consider deleting “bias” from this sentence. Bias may indeed be the cause of a large relative risk, just the wrong linkage.

- p.xxi-xxii, lines 75-14: Causation standard descriptors relating epidemiological information to causation.
  - Comment: Causation analysis inherently requires the package of considerations, from epidemiology, to bioassays, to mode of action, to … the Hill criteria. Yet, here, EPA is imputing causation analysis based on only the epidemiological parameter. Has EPA used these “epidemiological causation” descriptors before? One way to remedy would be to simply delete the words “consistent with causation” and leave the “association” terminology intact, because that is what is generally being addressed in such summaries of the epidemiological information.
- p. xxii, lines 68-71: “Negative results carry less weight, partly because they cannot exclude the possibility of effects in other tissues (IARC, 2006).”
  - Comment: Why should negative results carry less weight? I think that the genetic toxicology assessment should evaluate the results as a whole, and not pre-judge the validity of negative genetic toxicity studies. Indeed, to be balanced, EPA might also note publication bias against negative studies.
- p. xxiii, lins 9-11: “Toxicodynamic processes that lead to a health effect at this or another site (also known as mode of action).
  - Comment: Does mode of action not include any consideration of toxicokinetics, which this section implies? What about metabolism leading to toxic moieties, is this not part of the mode of action? Or (de)activation through stomach acids?
- p.xxiii, line 24: Suggest adding “Although important, information on mode of action is not required for a conclusion that the agent is causally related to an effect, in circumstances where there is compelling information supporting such a conclusion.”
- p. xxiii, lines 77-81: “It should be noted that in clinical reviews, the credibility of a series of studies is reduced if evidence is limited to studies funded by one interested sector (Guyatt et al., 2008a).”
  - Comment: This is a questionable statement. Evaluations should be based on rigor of study design, reproducibility, etc. not funding source. One could cite HHS (NIH or NTP) or EPA as interested sector funding sources.
- p.xxvi, lines 65-67: “For chronic effects, daily exposures are averaged over the lifespan.”
  - Comment: This is puzzling. Wouldn’t it be more accurate to say that “For chronic effects, daily exposures are averaged over the duration of the study, and assumed to continue over a lifespan in the modeling.”
- p. xxviii, lines 35-37: “Nonlinear approaches generally should not be used in cases where mode of action has not ascertained.”
  - Comment: Missing “been” between “has not” and “ascertained.”

Primary Comments

- Table 2-3, Figure 2-1, Table 2-7, Figure 2-2 – PODs and Candidate reference values: can you footnote (or add a column) that highlights which values are derived from oral/inhalation studies and which are from route-to-route extrapolation from inhalation to oral/oral to inhalation? It is confusing.
- p.2-28, line 28: "A candidate RfC for the same endpoint of urothelial hyperplasia based on route-to-route 27 extrapolation from the oral study (Suzuki et al., 2012; JPEC, 2010a) is 6 mg/kg-day…"
    - Comment: the units for 6 should be 6 mg/m^3.

Comments on Charge to the SAB

- Follow-up to question 3c: 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?