OMB Comments on EPA IRIS Toxicological Review of Trimethylbenzenes
June 27, 2016

Thank you for the opportunity to comment on the final draft Toxicological Review of Trimethylbenzenes in the Interagency Review process (Step 6b). I would like to respectfully request a conference call to discuss the items that I've identified below that would benefit from an interagency discussion. The page and line numbers are from the document titled "TMB_IASD Tox Review_6-1-16_compare to ERD draft" (the tracked changes version).

- Preamble lacks specific references (throughout) to existing EPA guidances as recommended by the SAB report.
- p.xxxiv line 93: there should be an explanation that cancer values for agents with suggestive evidence are meant to be used only for providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities as described in the 2005 Cancer Guidelines.
- p.xxxv line 21: is there an explanation of "studies of low sensitivity"?
- p.xxxvi line 42-44: is "the extra risk for…1% for human data" a standard policy? Please cite the reference.
- p.xxxvi line 57-67: The statement, "An *oral slope factor* or an *inhalation unit risk* facilitates subsequent estimation of human cancer risks at low levels of exposure. They presuppose a linear component to the dose–response curve below the point of departure (e.g., if the mode-of-action involves mutagenicity), or there may be no established mode-of-action" does not accurately convey section 3.3.1 of the EPA Cancer Guidelines, "the approach for extrapolation below the observed data considers the understanding of the agent's mode of action at each tumor site…When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained." Linear extrapolation is a health-protective approach that is used when there are insufficient data on the mode of action but it is not "presupposed."
- p.xxxvii line 5-7: The statement, "Calculation of reference values starts with a point of departure, generally for an early effect that precedes overt toxicity" does not accurately reflect current EPA guidance on reference value derivation. Reference values evaluate "adverse" health effects; there is no specific recommendation that an 'early effect that precedes overt toxicity' should be used for calculation of a reference value.
- p.xlii line 7-10: The statement, "It should be noted that the subchronic RfC values for the developing fetus are identical to the chronic RfC values as gestation represents a critical window of susceptibility and no UFS was applied to account for less than chronic exposure in either case" is confusing. The subchronic RfC value for the developing fetus is 4 mg/m3 (according to Table ES-2); the chronic RfC is 0.06 mg/m3 (Table ES-1). The statement should read "…subchronic values for the developing fetus are identical to the chronic RfC values for the *developing fetus* as gestation…" I think that is the correct comparison that EPA intends.