

**National Toxicology Program (NTP) Comments on the Interagency Science Consultation Draft IRIS
Assessment of ETBE (dated September 2014)**

Date: November 21, 2014



NATIONAL TOXICOLOGY PROGRAM
Department of Health & Human Services

NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES
111 T.W. ALEXANDER DRIVE
P.O. BOX 12233
RESEARCH TRIANGLE PARK, NC 27709-2233

MEMORANDUM

Date: November 18, 2014

To: Ron Milam, MPH, CFMS
Environmental Health Officer
Office of the Assistant Secretary for Health

From: Michael DeVito, Ph.D.
Acting Chief, National Toxicology Program Laboratory

Subject: **ETBE Toxicological Review**

This document was reviewed by Natasha Catlin, Ph.D., Georgia Hinkley, Ph.D. and Michael DeVito, Ph.D. from the NTP.

1. Literature search/study selection. Is the literature search strategy well documented? Please identify additional peer-reviewed studies that might have been missed.

We have reviewed the literature search strategy and believe it is well documented. We have found no additional peer-reviewed studies.

2. Physiologically-based pharmacokinetic (PBPK) modeling. In Appendix B, the draft assessment describes the development of an EPA PBPK model for ETBE in rats that also incorporates the PBPK model for *tert*-butanol. This model was adapted from published models for MTBE and *tert*-butanol (Blancato et al., 2007; Leavens and Borghoff, 2009).

2a. Does this PBPK model adequately represent the toxicokinetics? Are the model assumptions and parameters clearly presented and scientifically supported? Are the uncertainties in the model structure appropriately considered and discussed?

The model is adequately described and the assumptions and parameters are clearly presented and supported

2b. The concentration of *tert*-butanol in the blood was selected as the dose metric for route-to-route extrapolation for noncancer oral and inhalation points of departure (PODs). For the derivation of an oral slope factor, the rate of metabolism of ETBE was selected as the dose metric. Are the choices of dose metrics appropriate? Does this PBPK model adequately estimate the internal dose of *tert*-butanol in rats exposed to ETBE?

The choice of dose metric was tert-butanol blood concentrations. While this hypothesis is consistent with the data, it would be interesting to compare the results of this dose metric to tert-butanol alone. The EPA is developing a quantitative risk assessment for tert-butanol. Do you get the same dose response relationship for tert-butanol blood concentrations and kidney effects with both chemicals? This analysis would provide an interesting approach to evaluate the hypothesis that the tert-butanol alone accounts for the toxicity of ETBE.

The model does adequately describe the internal dose of tert-butanol in rats exposed to ETBE.

3. Hazard identification. In section 1, the draft assessment evaluates the available human, animal, and mechanistic studies to identify the types of toxicity that can be credibly associated with ETBE exposure. The draft assessment uses EPA's guidance documents (see <http://www.epa.gov/iris/backgrd.html/>) to reach the following conclusions.

3a. Kidney toxicity (section 1.1.1, 1.2.1). The draft assessment concludes that kidney toxicity is a human hazard of ETBE exposure. Do the available human, animal, and mechanistic studies support this conclusion, giving due consideration to the mode of action analyses for alpha_{2u}-globulin nephropathy and chronic progressive nephropathy?

We agree with EPA that the available data do not provide sufficient proof that binding to α_{2u} -globulin is the sole mechanism of the kidney lesions observed in the present study.

3b. Other types of toxicity (sections 1.1.2, 1.1.3, 1.1.5, 1.2.1). The draft assessment concludes that the evidence does not support other types of noncancer toxicity as a potential human hazard. Are there other types of noncancer toxicity that can be credibly associated with ETBE exposure?

The EPA has adequately described all the potential hazards associated with ETBE.

3c. Cancer (sections 1.1.1, 1.1.2, 1.1.4, 1.2.2). The draft assessment concludes that there is "suggestive evidence of carcinogenic potential" for ETBE by all routes of exposure. Do the available human, animal, and mechanistic studies support this conclusion, giving due consideration to the mode of action analyses for alpha_{2u}-globulin nephropathy, chronic progressive nephropathy, liver nuclear receptor-mediated effects, and acetaldehyde-mediated genotoxicity?

The EPA clearly describes their consideration and rejection of a mode of action that only considers alpha_{2u}-globulin nephropathy in the development of the kidney lesions and tumors.

4. Dose-response analysis. In section 2, the draft assessment uses the available human, animal, and mechanistic studies to derive candidate toxicity values for each hazard that is credibly associated with ETBE exposure in section 1, then proposes an overall toxicity value for each route of exposure. The draft assessment uses EPA's guidance documents (see <http://www.epa.gov/iris/backgrd.html/>) in the following analyses.

4a. Oral reference dose for effects other than cancer (section 2.1). The draft assessment proposes an overall reference dose of 5×10^{-1} mg/kg-d based on urothelial hyperplasia of the kidney. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, route-to-route extrapolation, and applying uncertainty factors?

This value is scientifically supported and gives appropriate consideration to the intermediate steps of selecting studies for dose-response analysis and calculating points of departure, provided that the dose response relationships for tert-butanol blood concentrations vs tumors are similar for ETBE and tert-butanol alone.

4b. Inhalation reference concentration for effects other than cancer (section 2.2). The draft assessment proposes an overall reference concentration of 9 mg/m³ based on urothelial hyperplasia of the kidney. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, and applying uncertainty factors?

This value is scientifically supported and gives appropriate consideration to the intermediate steps of selecting studies for dose-response analysis and calculating points of departure, provided that the dose response relationships for tert-butanol blood concentrations vs tumors are similar for ETBE and tert-butanol alone.

4c. Oral slope factor for cancer (section 2.3). The draft assessment proposes an oral slope factor of 9×10^{-4} per mg/kg-d based on liver tumors in rats, using a PBPK model to extrapolate the inhalation point of departure to an oral point of departure. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis and calculating points of departure, and route-to-route extrapolation?

This value is scientifically supported and gives appropriate consideration to the intermediate steps of selecting studies for dose-response analysis and calculating points of departure, provided that the dose response relationships for tert-butanol blood concentrations vs tumors are similar for ETBE and tert-butanol alone.

4d. Inhalation unit risk for cancer (section 2.4). The draft assessment proposes an inhalation unit risk of 8×10^{-5} per mg/m³ based on liver tumors in rats. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis and calculating points of departure?

This value is scientifically supported and gives appropriate consideration to the intermediate steps of selecting studies for dose-response analysis and calculating points of departure, provided that the dose response relationships for tert-butanol blood concentrations vs tumors are similar for ETBE and tert-butanol alone.

5. Executive summary. Does the executive summary clearly and appropriately present the major conclusions of the assessment?

The executive summary clearly and appropriately presents the major conclusions of the assessment