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

Date: November 19, 2014

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MEMORANDUM

Date: November 18, 2014

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

From: Michael DeVito, Ph.D.
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Subject: **Tert-butanol Toxicological Review**

This document was reviewed Jason Stanko, 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 *tert*-butanol in rats that was adapted from published models for MTBE (Blancato et al., 2007) and *tert*-butanol (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 EPA made several alterations to these models.

The discussion adequately describes the differences and limitations of the MTBE (Blancato et al) and tert-butanol (Leavens and Borghoff) models. First, the Leavens and Borghoff model described tert-butanol binding to α_{2u}-globulin. The EPA appropriately removed this binding from their tert-butanol model since the model provided adequate fits without this assumption. In addition, the EPA added a reversible protein binding in the blood to account for the fact that 60% of the radiolabelled tert-

butanol in whole blood is in plasma. However, since plasma is approximately 50-60% of whole blood it is not clear why this is necessary.

2b. The concentration of *tert*-butanol in the blood was selected as the dose metric to derive the BMCL. Is the choice of dose metric appropriate? Does this PBPK model adequately estimate the internal dose of *tert*-butanol in rats?

The model adequately describes blood concentrations of tert-butanol in rats and this is an appropriate dose metric.

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 *tert*-butanol 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 *tert*-butanol exposure. Do the available human, animal, and mechanistic studies support this conclusion, giving due consideration to the mode of action analyses for alpha2u-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. **Thyroid toxicity** (sections 1.1.2, 1.2.1). The draft assessment concludes that thyroid toxicity is a potential human hazard of *tert*-butanol exposure. Do the available human, animal, and mechanistic studies support this conclusion?

The evidence that thyroid hormone concentrations are altered by tert-butanol are available for only a single study that was less than 14 days. While this provides suggestive evidence that the increased follicular cell hyperplasia in the mice is due to changes in hormone levels, we concur with EPA that this evidence is weak.

3c. **Developmental toxicity** (sections 1.1.3, 1.2.1). The draft assessment concludes that there is suggestive evidence of developmental toxicity as a potential human hazard of *tert*-butanol exposure. Do the available human, animal, and mechanistic studies support this conclusion?

The evidence that tert-butanol is a developmental toxicant is weak and if it occurs at all is at doses of 1 g/kg/d, which are extraordinarily high and likely to be of limited human relevance.

3d. **Other types of toxicity** (sections 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 of *tert*-butanol exposure. Are there other types of noncancer toxicity that can be credibly associated with *tert*-butanol exposure?

3e. **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 *tert*-butanol 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 alpha2u-globulin nephropathy, chronic progressive nephropathy, and thyroid follicular cell tumors?

The EPA clearly describes their consideration and rejection of a mode of action that only considers alpha2u-globulin nephropathy in the development of the kidney lesions and tumors. In addition, the mode of action for the thyroid follicular cell tumors is adequately described and discussed.

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 *tert*-butanol 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 $1x10^{-1}$ mg/kg-d based on kidney transitional epithelial hyperplasia. 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.

4b. **Inhalation reference concentration for effects other than cancer** (section 2.2). The draft assessment proposes an overall reference concentration of $9x10^{-1}$ mg/m^3 based on kidney transitional epithelial hyperplasia, using a PBPK model to extrapolate the oral point of departure to an inhalation point of departure. 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.

4c. **Oral slope factor for cancer** (section 2.3). The draft assessment proposes an oral slope factor of $1x10^{-2}$ per mg/kg-d based on kidney 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.

4d. **Inhalation unit risk for cancer** (section 2.4). The draft assessment proposes an inhalation unit risk of $1x10^{-3}$ per mg/m^3 based on kidney tumors in rats, using a PBPK model to extrapolate the oral point of departure to an inhalation point of departure. 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 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.

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