



Draft IRIS Assessment of *tert*-Butyl Alcohol (*tert*-Butanol)

Presentation for the
ETBE and tBA Chemical Assessment Advisory Committee of
the Science Advisory Board
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Outline of Presentation

This presentation will cover:

- Summary of draft IRIS assessment for *tert*-butanol
- Address major questions raised during the July 11, 2016 teleconference
 - Evidence of toxicity for developmental, reproductive system, neurodevelopmental, liver, and urinary bladder described as “inadequate”
 - Rationale for the use of a drinking water study for deriving the RfC
 - Kidney endpoints are not relevant to human health because of α 2u-globulin and chronic progressive nephropathy (CPN)
 - Thyroid cancer in mouse only occurs at large doses, therefore not a concern for humans



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- *tert*-Butanol
 - Ethanol denaturant, metabolite of fuel additives (e.g. methyl- and ethyl-*tert*-butyl ether (MTBE and ETBE)), dehydrating agent and solvent, coating in metallic and paperboard food containers
 - Occupational exposures may occur at facilities where *tert*-butanol is produced
 - General population exposures may occur by ingestion of contaminated food from lined food containers; *tert*-butanol can be released into environmental media (air, water, soil) as a result of leaking underground storage tanks; ingestion of MTBE or ETBE
- Hazard identification – Noncancer
 - Kidney effects (increased organ weight, exacerbated nephropathy, transitional epithelial hyperplasia, and suppurative inflammation)
- Hazard identification – Cancer
 - *Suggestive evidence of carcinogenic potential* for *tert*-butanol. This is based on increased incidence of kidney tumors in male rats and primarily benign thyroid tumors in female and male mice following chronic oral administration.



RfD Derivation

Effect	Point of Departure (mg/kg-d)	UF	Chronic RfD (mg/kg-d)	Confidence
Kidney: Increases in severity of nephropathy in female rats NTP, 1995 2 year drinking water study in F344 rats	LOAEL: 43.2	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_L = 3$	4×10^{-1}	Medium
Overall Reference Dose (RfD) – Kidney			4×10^{-1}	Medium



RfC Derivation

Effect	Point of Departure (mg/m ³)	UF	Chronic RfC (mg/m ³)	Confidence
Kidney: Increases in severity of nephropathy in female rats NTP, 1995 2 year drinking water study in F344 rats	LOAEL _{HEC} : 491	Total UF = 100 UF _A = 3 UF _H = 10 UF _L = 3	5 x 10 ⁰	Medium
Overall Reference Concentration (RfC) – Kidney *			5 x 10 ⁰	Medium

*Derived from oral study, by route-to-route extrapolation



Summary of the Dose Response Analysis for Oral Cancer Data

Principal Study	Elevated tumor types	Extrapolation Method	Oral Slope factor _{HED} (mg/kg-d) ⁻¹
NTP (2005) 2-year drinking water study	Incidence of thyroid follicular cell adenomas and/or adenocarcinomas in female or male mice	3 ^o Multistage model with linear extrapolation from the point of departure (BMDL ₁₀)	5 x 10 ⁻⁴



Summary of the Dose Response Analysis for Inhalation Cancer Data

- Not determined
- No chronic inhalation studies are available
- Route-to-route extrapolation of mouse thyroid tumors is not possible because the only PBPK model available is for rats



Teleconference Questions



Hazard descriptions for hazards other than kidney and thyroid

- Evidence of toxicity for developmental, reproductive system, neurodevelopmental, liver, and urinary bladder is inadequate (Section 1.2 and Appendix B.2)
- “Inadequate” used if there is slight/indeterminate evidence in humans and animals (eg, lack of relevant studies, inconsistent results)
 - Developmental (Section 1.2.3)- fetal effects and maternal effects observed, no effects reported in one- and two-gen repro/dev studies on ETBE
 - Reproductive (Section 1.2.5)- inconsistent results
 - Neurodevelopmental (Section 1.2.4)- limitations in study design, reporting, or both; results not consistent between studies or across dose
 - Liver (Appendix B.2.1)- inconsistent results
 - bladder cancer (Appendix B.2.1)- inconsistent results



RfC derived from oral study

- Derived from oral study using route-to-route extrapolation (Section 2.2)
- No chronic inhalation study; only one 13-week study in rats and mice is available (NTP, 1997)
- Rat studies from both routes of exposure were considered for dose-response analysis
- Endpoint based on a longer duration and a more specific and sensitive indicator of kidney toxicity compared to kidney weight change

Table 2-6. Effects and corresponding derivation of candidate values

Endpoint (sex and species) and reference	POD _{HEC} ^a (mg/m ³)	POD type	UF _A	UF _H	UF _L	UF _S	UF _D	Composite UF	Candidate value (mg/m ³)
<i>Kidney</i>									
Increased absolute kidney weight at 13 weeks; female rat NTP (1997)	1137	NOAEL	3	10	1	10	1	300	4 × 10 ⁰
Increased absolute kidney weight at 15 months; female rat NTP (1995)	248	BMCL _{10%}	3	10	1	1	1	30	8 × 10 ⁰ *
Kidney inflammation (suppurative); female rat NTP (1995)	546	BMCL _{10%}	3	10	1	1	1	30	2 × 10 ¹ *
Kidney transitional epithelial hyperplasia; female rat NTP (1995)	920	BMCL _{10%}	3	10	1	1	1	30	3 × 10 ¹ *
Increases in severity of nephropathy; female rat NTP (1995)	491	LOAEL	3	10	3	1	1	100	5 × 10 ⁰ *

*These candidate values are derived using route-to-route extrapolated PODs based on NTP's chronic drinking water study.



Human relevance of kidney effects

- Mode of action analysis for kidney effects is presented in Section 1.2.1
- EPA determined that kidney tumors in male rats did not arise solely due to the α 2u-globulin (U.S. EPA, 1991) and CPN processes, and some of the tumors may be attributable to other carcinogenic processes
- CPN is a spectrum of lesions that could occur in a human kidney
- The individual lesions comprising the spectrum of lesions known as CPN could occur in a human kidney
- EPA considers CPN to be relevant for human health
- A written response to this public comment is provided in Appendix D
- Pathologists from both EPA and NTP reviewed the revised document



Human relevance of thyroid tumors

- Discussion of thyroid tumors as well as thyroid follicular cell hyperplasia and a potential anti-thyroid cancer MOA is presented in Section 1.2.2
- Incidence of thyroid follicular cell hyperplasia was elevated in treated male and female mice across the experimental treatment range (i.e. 510 - 2110 mg/kg-d)
- As the hyperplasia was considered to be a pre-neoplastic lesion, and would be a key precursor step in the progression of initiated thyroid follicular cells towards neoplasia, the presence of increased hyperplasia and/or neoplasia incidence in all treatment groups in both sexes of mice does not support the assertion that a threshold exists
- No MOA was identified and no mouse PBPK model is available
- A written response to this public comment is provided in Appendix D



Thank You!