Health-Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: October 2013
Expiration Date: October 2018

Toxicological Summary for Methyl tert-butyl ether (MTBE)

CAS: 1634-04-4

Synonyms: 2-Methoxy-2-methylpropane; Methyl tertiary-butyl ether; Methyl tert-butyl ether; Methyl t-butyl ether; MTBE; tert-Butyl methyl ether; tBME; tert-BuOMe

Note: Water contaminated with MTBE has a distinctive unpleasant odor and taste, detectable at concentrations below the MDH guidance value. The U.S. EPA has issued a drinking water advisory of 20-40 ug/L based on MTBE's organoleptic effects. The EPA advisory was developed to protect the consumer acceptance of the water source.

Acute Non-Cancer Risk Assessment Advice ($nRAA_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Risk Assessment Advice ($nRAA_{Short\text{-}term}$) = 700 ug/L

$$\frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.42 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 726 rounded to **700 ug/L**

Reference Dose/Concentration:	0.42 mg/kg-d (rats)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	500 mg/kg-d NOAEL (Williams, Cattley, and Borghoff, 2000)
Human Equivalent Dose (MDH, 2011):	500 x 0.25 = 125 mg/kg-d (male-specific HED for Sprague-Dawley rats at the subchronic duration)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty was applied due to a lack of oral studies examining developmental and reproductive endpoints.
Critical effect(s):	Increased kidney weight accompanied by histological changes
Co-critical effect(s):	Neurological effects such as anesthesia, hypoactivity, blepharospasms, ataxia, and lack of startle reflex; and changes in liver enzymes (decreased ALP and increased ALT and AST)
Additivity endpoint(s):	Hepatic (liver) system, Nervous system, Renal (kidney) system,

Subchronic Non-Cancer Risk Assessment Advice ($nRAA_{Subchronic}$) = Short-term nRAA = 700 ug/L

$$\frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.17 mg/kg/d) x (0.5)* x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 1104 rounded to 1000 ug/L

*MDH utilizes the U.S. EPA Exposure Decision Tree (U.S. EPA 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. A nonstandard RSC of 0.5 has been chosen for MTBE in order to take into account the potential for inhalation exposures from drinking water used for other activities.

Reference Dose/Concentration:	0.17 mg/kg-d (rats)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	209 mg/kg-d NOAEL (Bermudez, 2012)
Human Equivalent Dose (MDH, 2011):	209 x 0.24 = 50 mg/kg-d (male-specific DAF for Wistar rats at the subchronic duration)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty was applied due to a lack of oral studies examining developmental and reproductive endpoints.
Critical effect(s):	Increased kidney weight accompanied by histological changes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

The Subchronic nRAA must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nRAA is set equal to the Short-term nRAA of 700 ug/L. Additivity endpoints: Hepatic (liver) system, Nervous system, Renal (kidney) system

Chronic Non-Cancer Risk Assessment Advice ($nRAA_{Chronic}$) = Short-term nRAA = 700 ug/L

$$\frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.14 mg/kg/d) x (0.5)* x (1000 ug/mg)}}{\text{(0.043L/kg-d)}}$$

= 1628 rounded to 2000 ug/L

*See note about nonstandard RSC in subchronic duration.

Reference Dose/Concentration:	0.14 mg/kg-d (rats)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	140 mg/kg-d NOAEL (Dodd, Willson, Parkinson & Bermudez, 2013)
Human Equivalent Dose (MDH, 2011):	140 x 0.29 = 41 mg/kg-d (male-specific DAF for Wistar rats at

	the chronic duration)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty was applied due to a lack of oral studies examining developmental and reproductive endpoints.
Critical effect(s):	Increased kidney weight accompanied by histological changes
Co-critical effect(s):	Increased kidney weight accompanied by histological changes
Additivity endpoint(s):	Renal (kidney) system,

The Chronic nRAA must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nRAA is set equal to the Short-term nRAA of 700 ug/L. Additivity endpoints: Hepatic (liver) system, Nervous system, Renal (kidney) system,

Cancer Risk Assessment Advice (cRAA) = 60 ug/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.0018 \times 10 \times 0.137\ \text{L/kg-d} \times 2) + (0.0018 \times 3 \times 0.047\ \text{L/kg-d} \times 14) + (0.0018 \times 1 \times 0.039\ \text{L/kg-d} \times 54)] / 70}$$

= 57.02 rounded to **60 ug/L**

Cancer classification:	Animal carcinogen and possible human carcinogen.
Slope factor:	1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$ (rats) (based on renal tumors from Chun et al, 1992 (unpublished report aci in OEHHA, 1999))
Source of slope factor:	California Environmental Protection Agency 1999
Tumor site(s):	Kidney adenomas and carcinomas and Leydig cell tumors

Volatile: Yes (moderately volatile)

Summary of Guidance Value History: The MDH HBV of 70 µg/L was developed in 1999 based on California EPA's 1999 Public Health Goal (PHG). The current short-term, subchronic, and chronic noncancer HBV of 700 ug/L is based on studies published since the 1999 HBV was derived. The cancer HBV of 60 ug/L is based on the California EPA's 1999 PHG cancer slope factor. The new cancer HBV is lower than the previous HBV because it is based on cancer risk rather than kidney toxicity, and because of changes to methodology including the use of life stage adjustment factors and rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	No	Yes	Yes	No
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1] T_3 levels were increased at some time points after treatment with doses 30-90 times the short-term RfD (0.42 mg/kg-day). Another study showed that T3 levels decreased in response to MTBE exposure. Prolactin showed decreases after treatment with doses greater than 240 times the short-term RfD,

[2] In one study, at doses 175 times the RfD, neutrophils were significantly decreased, and lymphocyte counts were slightly elevated.

[3] No oral developmental studies have been completed at this time. Fetal skeletal abnormalities were noted in mice at more than 1000 times the short term RfD in an inhalation study. In a different inhalation study at a dose approximately 600 times the short-term reference dose, offspring exhibited decreased body weight gain.

[4] No oral reproductive studies have been completed at this time. In several inhalation studies, there were no reproductive effects reported in doses up to 1500 times the short term RfD. In one inhalation study increases in litters with malformations, skewed sex ratios, and total post-implantation losses were reported at a dose more than 2000 times higher than the short term RfD.

[5] Neurological effects were identified as co-critical effects. Hypoactivity, ataxia, blepherospasms, lacrimation, labored respiration, prostration, anesthesia, and lack of a startle reflex were noted in multiple studies at doses at least 300 times the short-term RfD.

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