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

Adopted as Rule: August 2018

Toxicological Summary for: Tetrahydrofuran

CAS: **109-99-9**
Synonyms: Oxolane; 1,4-Epoxybutane; THF

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 600 µg/L

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

$$= \frac{\text{(0.82 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 575 rounded to **600 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure an RSC of 0.2 rather than the default of 0.5 has been selected.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1.

Reference Dose/Concentration:	HED/Total UF = 82/100 = 0.82 mg/kg-d (Wistar rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	371 mg/kg-d (NOAEL, Hellwig et al. 2002)
Dose Adjustment Factor:	0.22 (body weight scaling, USEPA 2011)
Human Equivalent Dose (HED): (MDH 2011)	POD x DAF = 371 mg/kg-d x 0.22 = 82 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (oral data gaps include assessment of neurological effects and evaluation in a second species as limited oral data suggest rat may not be the most sensitive species)
Critical effect(s):	Decreased pup body weight gain, delayed eye opening
Co-critical effect(s):	Decreased pup body weight gain, decreased maternal body weight gain during gestation
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 600 µg/L

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

$$= \frac{\text{(0.82 mg/kg-d)}^{\#} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 2343 rounded to 2,000 µg/L

#The calculated Subchronic RfD (1.7 mg/kg-d) is higher than the Short-term RfD (0.82 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Subchronic RfD.

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 600 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 600 µg/L

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

$$= \frac{\text{(0.57 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 2591 rounded to 3,000 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1.

Reference Dose/Concentration:	HED/Total UF = 170/300 = 0.57 mg/kg-d (Wistar rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	714 mg/kg-d (NOAEL, Hellwig et al 2002, subchronic exposure in a 2 generation study)
Dose Adjustment Factor (DAF):	0.24 (body weight scaling, USEPA 2011)
Human Equivalent Dose (HED) (MDH, 2011):	POD x DAF = 714 mg/kg-d x 0.24 = 170 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation, and 3 for database uncertainty (oral data

	gaps include assessment of neurological effects and evaluation in a second species as limited oral data suggest rat may not be the most sensitive species)
Critical effect(s):	None (slight increase in relative kidney weight at NOAEL)
Co-critical effect(s):	None
Additivity endpoint(s):	None

The Chronic nHRL must be protective of the short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 600 µg/L. Additivity endpoints: Developmental

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	"Suggestive evidence of carcinogenic potential" by all routes of exposure (USEPA 2012)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Liver (female mice) and kidney (male rats) tumors following inhalation exposure. Oral cancer bioassays have not been conducted.

The modes of action for tumor induction by tetrahydrofuran are not well understood. The EPA Science Advisory Panel recommended that tetrahydrofuran is a weak, nongenotoxic carcinogen that would have a threshold. The chronic RfD (0.57 mg/kg-d) and the Short-term, Subchronic, and Chronic nHRL of 600 µg/L are adequately protective for cancer risk.

Volatile: Moderate

Summary of Guidance Value History:
A noncancer chronic HBV of 100 µg/L was derived by MDH in 1995. Short-term, Subchronic, and Chronic nHBVs of 600 µg/L were derived in 2016. The 2016 Chronic nHBV was higher than the 1995 chronic HBV as a result of: 1) using more recent toxicological data, 2) use of MDH's most recent risk assessment methodology, and 3) rounding to one significant digit. The 2016 guidance was adopted as HRLs in 2018.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
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. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	Yes	Yes	No
Effects observed?	-	-[1]	Yes[2]	No[3]	-[4]

Comments on extent of testing or effects:

[1] No oral studies assessing immunotoxicity have been conducted. Results from inhalation exposure studies do not provide consistent results, with some studies suggesting effects and others showing no effect. Decreased thymus weight and white blood cell counts have been reported in animals exposed to concentrations of ≥1770 mg/m^3. It is unclear whether these effects represent a functional effect on the immune system or represent a general stress response.

[2] Decreases in pup body weight gain and delayed eye opening was reported in both the one- and two-generation drinking water studies in rats. These effects form the basis of the Short-term RfD. Inhalation exposure of pregnant rats to concentrations of ≥5000 mg/m^3 resulted in decreased number of implants, decreased pup body weight, and delayed development.

[3] No effects on reproductive endpoints were reported in the one- or two-generation drinking water studies in rats at doses up to 200-fold greater than the Short-term RfD and ~300-fold greater than the Chronic RfD.

[4] Oral studies evaluating neurotoxicity have not been conducted. Signs of CNS (central nervous system) effects such as ataxia have been reported after bolus gavage dosing at doses ≥200-fold greater than the Short-term RfD and ≥300-fold greater than the Chronic RfD. An older study reported paralysis of hind limbs in animals following exposure to THF, but this study was poorly reported and the results are inconsistent with other better designed and reported studies.

Resources Consulted During Review:

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