



Toxicological Summary for: Tetrahydrofuran

CAS: 109-99-9

Synonyms: Oxolane; 1,4-Epoxybutane; THF

Acute Non-Cancer Health Based Value (nHBV_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBV_{Short-term}) = 600 µg/L

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

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

$$= 575 \text{ rounded to } \mathbf{600 \text{ µg/L}}$$

*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:	(POD x DAF)/Total UF = 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)
Human Equivalent Dose (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 Based Value (nHBV_{Subchronic}) = nHBV_{Short-term} = 600 µg/L

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

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

$$= 2343 \text{ rounded to } 2,000 \text{ } \mu\text{g/L}$$

[#]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 nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 600 $\mu\text{g/L}$. Additivity endpoints: Developmental

Chronic Non-Cancer Health Based Value (nHBV_{Chronic}) = nHBV_{Short-term} = 600 $\mu\text{g/L}$

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

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

$$= 2591 \text{ rounded to } 3,000 \text{ } \mu\text{g/L}$$

^{*}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:	(POD x DAF)/Total UF = 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)
Human Equivalent Dose (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 nHBV must be protective of the short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 600 $\mu\text{g/L}$. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Derived

Cancer classification: "Suggestive evidence of carcinogenic potential" by all routes of exposure (EPA 2012)

Slope factor (SF): Not Applicable

Source of cancer slope factor (SF): Not Applicable

Tumor site(s): Liver and kidney tumors in female mice and male rats, respectively, following inhalation exposure

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 nHBV 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 is 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. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process tetrahydrofuran would be scheduled for re-evaluation in 2021.

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/m³. 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/m³ 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:

- Australian Department of Health. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). (2015). Inventory Multi-tiered Assessment and Prioritisation (IMAP). Human Health Tier II Assessment for Furan, tetrahydro-. CAS Number: 109-99-9. Retrieved from http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=117
- California State Water Resources Control Board. (2011). Compilation of Water Quality Goals.
- Chhabra, R., RA Herbert, JH Roycroft, B Chou, RA Miller, RA Renne,. (1998). Carcinogenesis Studies of Tetrahydrofuran Vapors in Rats and Mice. *Toxicological Sciences*, 41, 183-188.
- Craig, E., Z Yan, QJ Zhao,. (2014). The relationship between chemical-induced kidney weight increases and kidney histopathology in rats. *Journal of Applied Toxicology*, 35, 729-736.
- European Chemicals Agency (ECHA). (2010). Committee for Risk Assessment (RAC) Annex 1 Background Document to the Opinion proposing harmonised classification and labelling at Community level of tetrahydrofuran (EC Number: 203-726-8; CAS Number: 109-99-9). Retrieved from http://www.echa.europa.eu/documents/10162/13579/annex1_background_document_thf_cas109-99-9_en.pdf
- Fenner-Crisp, P. A., Mark E. Mayes, Raymond M. David,. (2011a). Assessing the human carcinogenic potential of tetrahydrofuran: I. Mode of action and human relevance analysis of the male rat kidney tumor. *Regulatory Toxicology and Pharmacology*, 60, 20-30.
- Fenner-Crisp Penelope A., M. E. M., Raymond M. David. (2011b). Assessing the human carcinogenic potential of tetrahydrofuran: II. Mode of action and human relevance analysis of the female mouse liver tumor. *Regulatory Toxicology and Pharmacology*, 60, 31-39.
- Fowles, J., Rodney Boatman, Jim Bootman, Chris Lewis, David Morgott, Erik Rushton, Joost van Rooij, Marcy Banton. (2013). A review of the toxicological and environmental hazards and risks of tetrahydrofuran. *Critical Reviews in Toxicology*, 43(10), 811-828.
- Hejtmancik, M. (1982). *A repeated dose test with tetrahydrofuran (C60560) in B6C3F1 mice*. Gulf South Research Institute.
- Hejtmancik, M. (1983b). *A report on the prechronic test of tetrahydrofuran using B6C3F1 mice*. Gulf South Research Institute

- Hejtmanik, M. (1983a). *A report on the prechronic test of tetrahydrofuran using Fischer Rats*. Gulf South Research Institute.
- Hellwig, J., C. Gembardt, S. Jasti. (2002). Tetrahydrofuran: two-generation reproduction toxicity in Wistar rats by continuous administration in the drinking water. *Food and Chemical Toxicology*, 40, 1515-1523.
- Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. Support document relating to Health Risk Limits for Groundwater Rules. Retrieved from <http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf>
- Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. Retrieved from <http://www.health.state.mn.us/divs/eh/risk/guidance/hedrefguide.pdf>
- National Toxicology Program (NTP). (1998). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Tetrahydrofuran (CAS No. 109-99-9) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Retrieved from http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr475.pdf
- Texas Risk Reduction Program (TRRP). (2015). TRRP Protective Concentration Levels (PCLs) - Residential Retrieved from <http://www.tceq.texas.gov/remediation/trrp/trrppcls.html>
- Toxicology Excellence for Risk Assessment - ITER International Toxicity Estimates for Risk (ITER). Retrieved from http://iter.ctcnet.net/publicurl/pub_search_list.cfm
- U. S. Environmental Protection Agency (EPA). (2012). Toxicological Review of Tetrahydrofuran (CAS No. 109-99-9). In Support of Summary Information on the Integrated Risk Information System (IRIS). Retrieved from http://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1023tr.pdf
- U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Retrieved from <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855>
- U.S. Environmental Protection Agency - Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV). Retrieved from http://hhpprtv.ornl.gov/quickview/pprtv_papers.php
- U.S. Environmental Protection Agency. (2011). Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose. Retrieved from <http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf>
- U.S. Environmental Protection Agency (EPA) - Office of Research and Development. (2011). Exposure Factors Handbook: 2011 Edition. Retrieved from <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252>
- U. S. Environmental Protection Agency. (2000). Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. EPA-822-B-00-004. October 2000.
- U.S. Geological Survey - Health-Based Screening Levels. Retrieved from <http://infotrek.er.usgs.gov/apex/f?p=HBSL:HOME:0>